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Cancer

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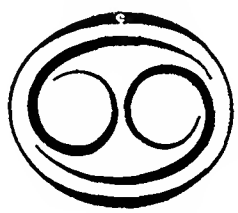

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Cancer

A Journal of the American Cancer Society

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BESONDERER RÜCKSICHT AUF DIE DAUERNDE HEILBARKEIT
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NACH BEOBACHTUNGEN

AN DER WIENER CHIRURGISCHEN KLINIK

DES

PROF. Dr TH. BILLROTH

VON

Dr ALEXANDER VON WINIWARTER,
PRIVATDOCENTEN FÜR CHIRURGIE AN DER UNIVERSITÄT WIEN

MIT EINEM VORWORT

VON

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VERLAG VON FERDINAND ENKE.
1878.

ALEXANDER VON WINIWARTER (1848-1916)

THE system of "follow up" and compilation of end results, so essential for the evaluation of therapeutic methods in the treatment of cancer, was introduced by Alexander von Winiwarter about sixty years ago. This pioneer surgeon and investigator reviewed all of the surgically treated cancer cases in Billroth's clinic during the period 1867-1876 and in a monumental monograph, statistically analyzed the records of 548 cancer patients. The concepts of cure rate by years and the clinical classification of tumors according to their anatomical sites may be largely attributed to his efforts. By demonstrating definite salvage rates, particularly for breast cancer following mastectomy, Winiwarter's comprehensive study had an enormous influence in spreading the credo that cancer is curable.

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CANCEROPHOBIA — NO NEW THING

IN 1734, the feminine world of Besançon succumbed suddenly to an epidemic of fear—fear of having, or of momentarily developing, cancer of the breast. Its germ was the recommendation of a "surgeon" to the women to examine their breasts for lumps. "Effrayées par un opérateur interessé ou peut instruit," says Vacher. They obeyed him so thoroughly, examining and pressing their breasts long and often, that a number of women actually developed lumps. These were operated upon immediately, and with the greatest success, by the "surgeon." (Wolff, Jacob. Die Lehre von der Krebskrankheit. Jena. G. Fischer. 1911; Vol. 2, p. 1101.)

NITROGEN-MUSTARD THERAPY FOR HODGKIN'S DISEASE, LYMPHOSARCOMA, THE LEUKEMIAS, AND OTHER DISORDERS*

MAXWELL M. WINTROBE, M.D. and CHARLES M. HUGULEY, JR., M.D.†

DURING World War I it was discovered that leukopenia may result from poisoning with mustard gas.[11] World War II saw the introduction of a series of compounds, the nitrogen mustards, that differ from mustard gas only in the replacement of sulfur by nitrogen. The biologic effects of these compounds parallel, and are in many respects identical with, those of roentgen rays.[4, 10] They exert a cytotoxic effect that is related to the proliferative activity of tissues and is particularly marked upon the hemopoietic tissue. This characteristic has led to the clinical trial of certain of these compounds in cases of neoplastic disease, especially the malignant processes involving chiefly the lymph nodes and bone marrow.[1, 5, 6, 7, 9, 13]

The chemistry and pharmacology of the nitrogen mustards have been described by Gilman and Philips,[4, 12] who have summarized the work of a large group of investigators that was carried out during World War II, the results of which are, for the most part, as yet unpublished. The action of the mustards depends upon intramolecular cyclization with the formation of a series of ethylene imonium compounds. The latter are highly reactive and are capable of alkylating a large number of biologically functional groups such as sulfhydryl, amino, imidazole, sulfide, carboxyl, pyrido-N, and organic phosphate. There is considerable evidence that by reacting with one or more such groups, the mustards produce a deleterious effect upon important intracellular protein. It is probable that the cytotoxic action is the result of inactivation of one or more cellular enzymes.

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* This study was aided by a grant from the American Cancer Society, on recommendation of the Committee on Growth, National Research Council.

† Fellow of the American Cancer Society.

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Doses of nitrogen mustard exceeding the MLD produce marked generalized effects. The action of smaller doses is most pronounced upon the more proliferative tissues. Complete dissolution of lymphoid tissue in animals has been produced within twenty-four hours.[10] The action upon the bone marrow is slower but may lead to complete aplasia. The gastrointestinal epithelium is next in order of susceptibility; in large doses mustard will produce a hemorrhagic enteritis.

Minimally effective doses produce a striking inhibition of mitosis. Resting cells and cells in active mitosis are not appreciably affected, but cells in the premitotic phase are arrested at that stage. Larger doses lead to nuclear fragmentation and dispersal of chromatin.[3]

The protective effect of temporary occlusion of the blood supply to sensitive tissues during and for a short period after the intravenous injection of nitrogen mustards demonstrates that the direct toxic action is completed in two to five minutes.[8] The compounds clinically studied have been methyl-bis (β-chloroethyl) amine HCl, known as HN_2, and methyl-tris (β-chloroethyl) amine HCl, known as HN_3.

METHODS AND MATERIAL

In these studies only the methyl-bis (β-chloroethyl) amine HCl (HN_2) has been used. This drug is obtained as a dry powder in small, sterile bottles containing 10 mg. It is readily soluble. Ten ml. of normal saline are injected into the bottle and the desired aliquot removed. This is injected rapidly through the tubing of an intravenous infusion of saline. The drug must be used promptly after being put into solution, since its activity is quickly dissipated in this state. We have found administration of nitrogen

mustard through a saline infusion to be quite effective in preventing phlebothrombosis and extravasations. Since the drug is a vesicant, care must be taken to avoid spilling it on the skin or mucous membranes. However, no harm has resulted from accidental spilling if the material has been washed off with reasonable promptness.

Dosage. In most instances a dose of 0.1 mg. per Kg. of body weight has been used. Ordinarily this dose has been administered at daily intervals, four to six injections constituting a course of therapy. In several cases of acute leukemia, therapy has been instituted with doses of 0.025 or 0.05 mg. per Kg. On the other hand, when the usual dose has been well tolerated, the number of injections has been decreased by increasing the amount injected per dose to 0.2 or even 0.3 mg. per Kg. In chronic myelocytic leukemias with very high leukocyte counts as much as 0.8 mg. per Kg. has been used for the initial course. In other conditions the maximum total dose has been limited to 0.6 mg. per Kg.; *and if leukopenia, thrombocytopenia, or* marked anemia have been present, no more than 0.4 mg. per Kg. has been given.

Courses of therapy have been repeated as often as symptoms have recurred, usually in two or three months, sometimes at much longer intervals. We do not deem it advisable to repeat a full course in less than four weeks.

In chronic myelocytic leukemia, best results have been obtained by giving doses of 0.15 to 0.2 mg. per Kg. every two or three weeks, depending upon the total leukocyte count and the general condition of the patient, the object being to keep the count at a low level and to prevent the appearance of symptoms.

Physical and Laboratory Examinations. Patients selected for therapy with HN_2 have received the usual examinations and whatever special procedures have been necessary to determine the nature and extent of the disease process. Except in the cases of leukemia and in certain of those included in the miscellaneous group in which adequate biopsy material could not be obtained, the diagnosis has been established by biopsy. Hematological studies have included red-cell counts, hemoglobin and hematocrit determinations, total and differential white-cell counts, and platelet counts. In many instances bone-marrow studies have been made. Tourniquet tests and determinations of bleeding time and clot-retraction time have been made when indicated.

In most instances it has seemed desirable to hospitalize the patient for the first course of HN_2. Many required frequent and prolonged hospitalization. If the drug was well tolerated and the condition of the patient did not require further hospitalization, subsequent courses frequently were administered as an office procedure.

During the earlier part of this study, determinations of the total and the differential leukocyte counts were made every two days and the volume of packed red cells and the number of platelets were measured twice a week. Such frequent examinations are not necessary, however. During the past year, a hematocrit determination, the total and differential leukocyte count, and a platelet count have been made one week after the initiation of therapy and twice a week for the next two weeks in uncomplicated cases. Studies have been made more frequently, often daily, in those patients who exhibited severe anemia, thrombocytopenia, or leukopenia prior to treatment, or who developed such manifestations following treatment. At the same intervals, an attempt was made to quantitate physical findings, particularly the size of the lymph nodes, liver, and spleen.

After the first three weeks subsequent to therapy the patients and their blood have been examined at such intervals as have been indicated by the status of the disease. In those who have responded well this has been once every month, occasionally every two months, or even less often. The foregoing applied chiefly to patients with Hodgkin's disease or lymphosarcoma. As already stated, patients with leukemia were treated at short intervals.

General symptomatic and supportive measures have been used as indicated and transfusions of whole blood given to those with anemia severe enough to necessitate them. The status of the disease process has been

followed by frequent roentgenographic studies in patients with involvement of the lungs, mediastinum, bone or intestine.

Patient Material. In all, 102 patients have been treated and observed for periods of three to thirty-three months. For statistical data concerning these patients see Table 1.

Of the entire group of 102 patients, 31 are living at the time of this writing. Of these, 16 have been followed for a year or more (maximum thirty-three mos.) since receiving their first treatment. Of the 71 patients who are now dead, only 10 were observed for nine months or more.

Clinical Results

In the series of 102 patients, there are 85 with Hodgkin's disease, lymphosarcoma, reticulum-cell sarcoma, or leukemia. Almost all stages and manifestation of these diseases are represented. The other 17 patients comprise a miscellaneous group of disorders. The important data concerning each patient are summarized in Tables 2 to 8.

Criteria of Evaluation. We have attempted to evaluate the effect of HN2 as *good, fair,* or *poor.*

The response has been classified as *good* when the patient was enabled to return to his usual occupation for a period of six months or more. In some instances, anatomical evidences of disease did not disappear, and functional impairment due to such changes persisted, because the disease damage was of such a character (e.g., scar tissue) that disappearance of the anatomical changes could not be expected. When such patients were kept comfortable and free of incapacitating symptoms for six months or more, the response has also been termed *good* even though they were unable to return to their previous activities.

When the patient had comparable improvement for a shorter period, or had fair symptomatic improvement for approximately six months, or had marked relief of a serious symptom even though the course of the disease was not altered (e.g., bone pain in acute leukemia), the response has been termed *fair.*

When improvement was short-lived or slight, the response has been classified as *poor.* In the following discussion we shall attempt only to elucidate and emphasize certain features of special interest.

Hodgkin's Disease. Thirty-two patients with this disease have been treated. Of these, thirteen are still living, an average of fifteen months since the initiation of therapy and thirty-six months since the onset of symptoms. All have been observed for at least six months since treatment was started, and nine have been followed for a period of twelve months or longer. The nineteen patients who are dead lived an average of eight months after HN2 was first given and thirty-two months after the onset of symptoms. Four were followed for a year or longer, one for twenty-nine months.

Twenty-six of these patients had had previous roentgen-ray treatment, and of these thirteen had shown a poor response or had reached a stage where such therapy was no longer effective or no longer tolerated. Of these thirteen, the response to HN2 was good in five, and one, still living after twelve months, has had a fair response. In seven, the administration of HN2 showed no advantage when compared with roentgen-ray therapy.

We have evaluated the response of the whole series of thirty-two patients as *good* in seventeen, *fair* in five, and *poor* in ten. Those who have responded well have needed subsequent treatment in an average of three months' time; however, the remissions induced have ranged from four weeks to twenty-six months, usually two to five months.

Three of these patients were considered by pathological examination to have Hodgkin's sarcoma. None was responding to roentgen-ray therapy when HN2 was first given, and all three died in three months without having exhibited any evidence of benefit from the therapy.

Fever. One of the most constant and striking effects of HN2 therapy in Hodgkin's disease has been upon the fever in those patients manifesting it (Fig. 1). Except for one case of Hodgkin's sarcoma and one terminal case with secondary infection, the first course of HN2 has caused the temperature to return

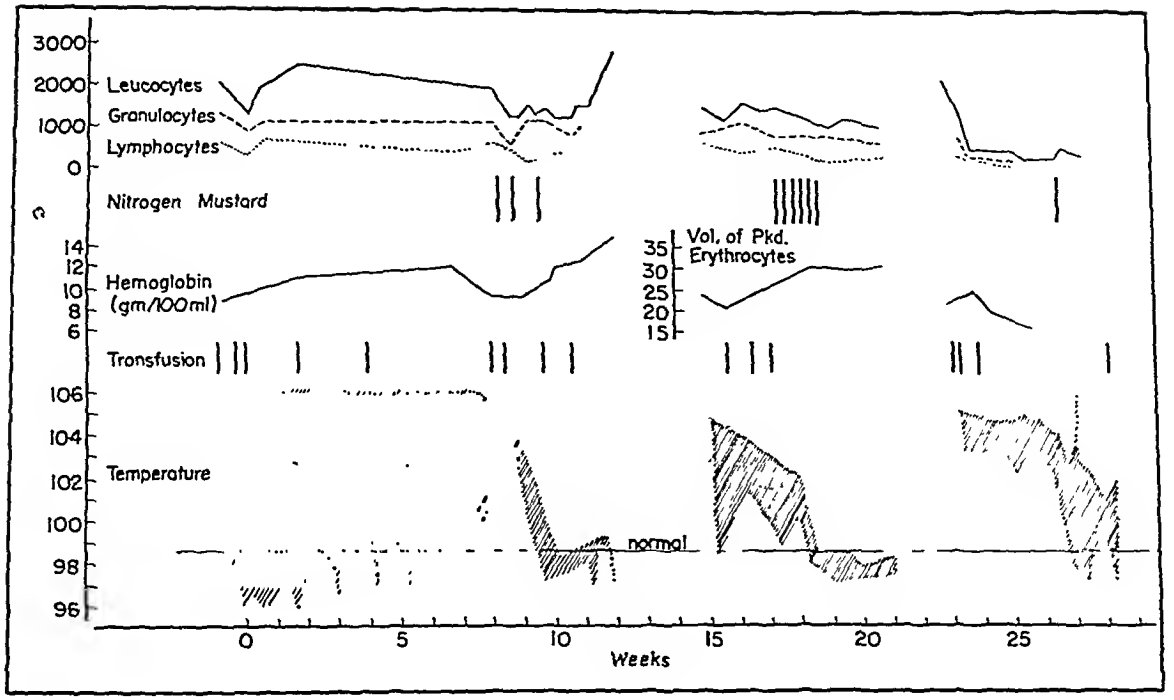

FIG. 1. *Course of a patient (case 15) with Hodgkin's disease whose fever, ranging from 106° to 96° daily, ceased abruptly following three injections of nitrogen mustard. This treatment, however, became less and less effective and the patient ultimately died.*

to normal, and in many patients this effect was repeated in subsequent courses. In all but two patients this return of the temperature to normal occurred in two days or less after the first dose of the drug.

In most of those patients who responded well and in some who had only transient benefit, improvement began within five to ten days after the first dose. Frequently this improvement was very dramatic with an upsurge of feeling of well-being and a remarkable improvement in appetite. Gain in weight and general clinical improvement followed.

ENLARGED NODES. Most of our patients had received several courses of roentgen-ray therapy before they came to us, so that markedly enlarged lymph nodes seldom formed a prominent part of the clinical picture. When present, enlarged nodes usually decreased very definitely and symptoms due to pressure were reduced. However, it has been seldom that all superficial nodes have disappeared completely. The same can be said for splenomegaly although in a number of cases a spleen that was easily palpable before therapy was not palpable afterwards. Figure 2 illustrates the rapidity with which marked changes in the size of the spleen may take place.

In this series, the chest roentgenograms of twenty patients were interpreted as showing involvement of mediastinal lymph nodes or

FIG. 2. *Reduction in the size of the spleen following nitrogen-mustard therapy in a case of Hodgkin's disease (case 15). The course of this patient is illustrated in Fig. 1.*

lung parenchyma, or both. Usually, mediastinal nodes did not produce serious symptoms and decreased in size following therapy. However, in seven patients the pulmonary involvement was quite serious. Good results have been achieved in several.

One patient (case 16) had a mass in the left upper lobe with cavitation, which obstructed the bronchus (Fig. 3). Despite good general improvement following two courses of HN_2, the mass did not change and the abscess was drained surgically. The wall of the abscess proved to be made up of Hodgkin's tissue. After drainage, 800 r of roentgen-ray therapy to the area, and another course of HN_2, she showed excellent improvement. Subsequently, the enlargement of the mediastinal nodes, with obstructive symptoms, recurred repeatedly, but each time the patient recovered after HN_2 or roentgen-ray therapy. She received twelve courses of HN_2 and nine courses of roentgen-ray therapy without evidence of cumulative toxicity. On the whole, HN_2 seemed to be more effective than roentgen-ray therapy. The last course was given because of atelectasis of the left lung. This had cleared when she died suddenly while at home, sixteen days later and twenty-eight and a half months after the first course of HN_2. Death was due to aspiration pneumonia following the development of a tracheoesophageal fistula, perhaps produced by a stomach tube that had been retained for forty-eight hours.

Another patient (case 18) had extensive involvement of the lung parenchyma that was no longer affected by roentgen-ray therapy. There was remarkable clearing after HN_2. Ten months later, despite intervening treatment with HN_2, he again developed extensive changes. Again he showed marked clearing following a combination of roentgen-ray and HN_2 therapy. This patient eventually became refractory to both agents and died sixteen months after the first HN_2 therapy, but his condition prior to the institution of such treatment was such that he surely would have succumbed much sooner had he not received mustard.

A 14-year-old girl (case 52) with cough, dyspnea, and dysphagia was found to have atelectasis of the right lower lobe due to parenchymal involvement and pressure from mediastinal nodes. Roentgen-ray therapy had produced temporary improvement initially but was later ineffective. She has had four courses of HN_2, the last five months ago, and is now feeling better than at any time since the onset eighteen months ago, although atelectasis of the right lower lobe is still present.

In other cases the improvement has been less striking or did not occur.

Back Pain. This has been the chief symptom in four patients.

Case 3 was in the terminal stages and HN_2 was without effect upon a paraplegia and anesthesia below the level of the fourth rib.

Case 23 had severe back pain attributable to a pathological fracture of the fourth lumbar vertebra. Following HN_2, there was complete relief of pain and tenderness and some

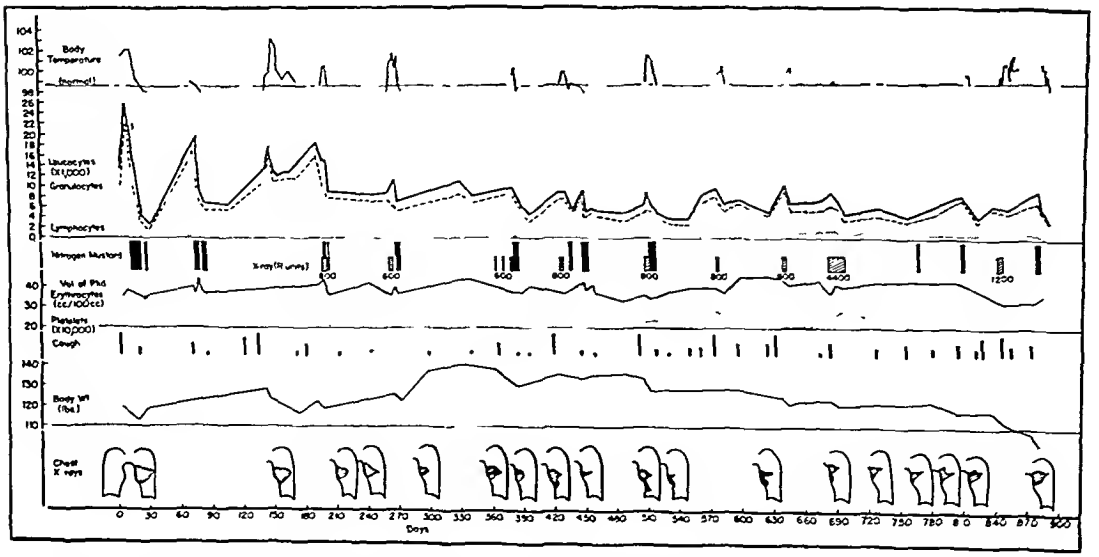

Fig. 3. *Course of a patient (case 16) with Hodgkin's disease under nitrogen-mustard and roentgen-ray therapy. For details see text and Table 3.*

roentgenographic evidence of healing. She received no more therapy and the back pain recurred shortly before death six months later.

Case 73 had back pain and weakness of the lower extremities that had progressed despite a course of roentgen-ray therapy. There was erosion of the eleventh thoracic vertebra and a block of the spinal canal. He has received two courses of HN_2 one month apart, and is now living with no symptoms or signs of illness ten months after the initiation of therapy.

In case 62, back pain is the chief complaint, and in cases 42, 67, and 69, it has been one of the symptoms. There has been no roentgenographic evidence of spinal involvement in any of these cases. In all there has been relief of pain following therapy.

ABDOMINAL PAIN. In two patients this has been the chief complaint.

In one (case 67) small-bowel involvement was demonstrated radiologically. The pain and the radiological evidence disappeared after therapy. Subsequent recurrences have been successfully controlled, and the patient is at present asymptomatic ten months after the first treatment.

In the other patient (case 63), one of the three with Hodgkin's sarcoma, large abdominal masses were present. The pain was quickly relieved after HN_2 administration, but the improvement was short-lived.

PRURITUS. In only four patients has pruritus been a distressing problem. In two, it disappeared when general improvement took place; in one of these, it was associated with a severe dermatitis with excoriations, caused by scratching. In the other two, the disease was in its terminal stages when this symptom appeared, and neither the pruritus nor the general condition of the patients was improved by HN_2.

CELLULAR ELEMENTS OF THE BLOOD. When there was a good general response to HN_2 therapy, these elements of the blood returned to normal. We have not found anemia, leukopenia, or thrombocytopenia to be contraindications to therapy with HN_2. On the contrary, they may be interpreted as indicating the need for treatment.

The hematological effects of the administration of HN_2 to patients with normal blood counts are described later. In nineteen of the patients with Hodgkin's disease, anemia was present prior to therapy. In seven of these, the red-cell level returned to normal. In some instances this was quite striking.

One patient (case 18) who had required repeated transfusions maintained a normal red-cell count for ten months after the initiation of HN_2 therapy.

Another patient (case 4) with hemolytic crises and severe anemia despite frequent transfusions was able to maintain a nearly normal red-cell level for two months after HN_2 was first administered.

Leukopenia was present in six patients before treatment was begun and in three of these the leukocyte count returned to normal at least temporarily after HN_2. The platelet count returned to normal after treatment in all of 5 patients who exhibited thrombocytopenia before therapy. In these cases no more than 0.4 mg. per Kg. has been given in a single course to a patient.

In the foregoing we have discussed patients with serious symptoms. Six of those with Hodgkin's disease (cases 33, 42, 47, 61, 69, and 85) had minimal symptoms — chiefly malaise, moderate weight loss, and lymphadenopathy. Episodes of fever were the only complaints in case 27. All of these patients have shown a good response to mustard therapy and are still living six to twenty-two months after its initiation. Remissions between courses have varied from one to twelve months and have averaged four months.

Lymphosarcoma. Eleven patients with this disease have been treated. Of these only two are living, thirteen and four months, respectively after the initiation of therapy with HN_2. The other nine are dead. They lived an average time of only five and four-tenths months after HN_2 therapy was begun and thirty-four months after the onset of symptoms.

The response has been good in 3 patients.

In case 9, the disease originally involved the maxilla. Later a laparotomy was performed and a liver abscess drained; its wall was composed of lymphosarcomatous tissue. A good response to HN_2 occurred, and the patient felt well until twelve months later, when he died of peritonitis following rupture of the small bowel. At autopsy the perforation proved to be caused by involvement of the intestinal wall by lymphosarcoma. Interestingly enough, there was no longer any evidence of infiltration of the liver.

Case 51 exhibited a slow decrease in the size of involved lymph nodes, but at the present time the patient enjoys exuberant health thirteen months after a single course of HN_2.

Case 65 was benefited initially but ultimately responded poorly to treatment and is now dead, eleven months after his first HN_2 injections.

Case 98, treated only four months ago, showed a rapid and marked decrease in the size of the involved lymph nodes and tonsils, but the response was short-lived. Two subsequent courses were effective for even shorter periods of time and he was changed to roentgen-ray therapy. The effect on the adenopathy was striking but again only temporary.

All of the other patients exhibited little, if any, change after HN_2 therapy.

Reticulum-Cell Sarcoma. Of five patients with this disease, only one showed a good response and all are dead. They lived an average of three and four-tenths months after first receiving HN_2 and eleven months after the onset of symptoms.

In case 26 a large neck mass decreased rapidly in size in a period of two weeks and there was general improvement (Fig. 4). However, she failed to return for further therapy and died ten months after the initial course.

Leukemia. Eleven patients with chronic myelocytic leukemia have been treated. Seven are living an average of sixteen months after the beginning of HN_2 therapy. and thirty months after the appearance of symptoms. Four of these have been followed for more than one year and three for two years or more. Four patients died one to four and a half months after HN_2 was begun and thirty-seven to fifty-three months after the onset of symptoms. With the exception of one patient who has had the disease for seven years and one who has had it for thirty-eight months, none of the patients now living has been ill for more than three years; whereas all of the patients now dead had been known to have had the disease for more than three years.

All of the patients now living have shown a good response to therapy and are following their usual occupations.

One of them (case 22) received HN_2 for fourteen months and was doing well (Fig. 5). In the past twelve months she has been treated with urethane. She has been asymp-

FIG. 4. *Disappearance of adenopathy in the neck following nitrogen-mustard therapy in a case of reticulum-cell sarcoma (case 26). The second photograph was taken twelve days after the first.*

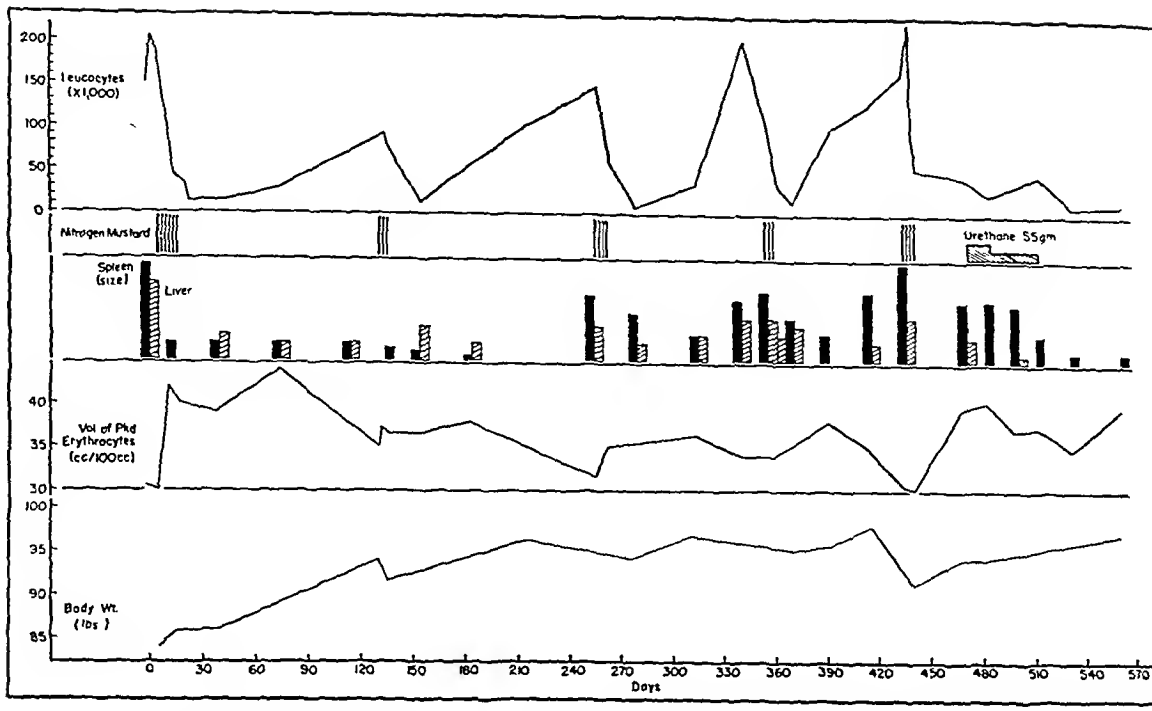

FIG. 5. *Course of a patient with chronic myelocytic leukemia (case 22) under nitrogen-mustard and, later, urethane therapy.*

tomatic while on this drug and requires very small doses.

Another (case 44) received HN_2 for six months and has been treated with urethane for seven months. The systemic and hematological response to the two drugs has been about the same, but the patient prefers urethane because of the nausea he suffers from the injection of HN_2.

A third patient (case 31) has had a trial with both drugs but showed a very poor response to urethane whereas she has been asymptomatic under HN_2 therapy for twenty-three months after her first treatment.

The other patients in our series of living cases have received only HN_2.

Of the four patients now dead, all had received roentgen-ray therapy prior to HN_2 and all had responded well but eventually became refractory. At this stage they failed to obtain lasting benefit from HN_2.

One of them (case 56) showed a dramatic feeling of well-being following HN_2 therapy for a period of two months, together with a marked decrease in the leukocyte count, but failed to respond to a second course when his symptoms returned.

The other three received little or no benefit from HN_2 or urethane.

The five patients who are still receiving HN_2 therapy are being given doses of 0.1 to 0.2 mg. per Kg. at frequent intervals, depending upon the white-cell count. Two receive an average of 0.2 mg. per Kg. every two weeks, two receive 0.2 mg. per Kg. every three weeks, and one receives 0.1 mg. per Kg. every two weeks. On this schedule they have remained asymptomatic and have suffered only mild inconvenience from the therapy. Their white-cell counts remain reasonably low and their red-cell counts and weights remain at normal levels.

In the seven patients who responded well to HN_2, there was moderate to marked regression in the size of the spleen. In two, a spleen filling the entire left side of the abdomen shrank to a position only one to two finger breadths below the costal margin. In six cases the liver was palpable. It is no longer palpable in three, and in only one has it failed to regress markedly in size. We have seldom been able to palpate any superficial lymph nodes after treatment has been started.

Invariably, following therapy there has been a drop in the leukocyte count followed by a steady rise in the volume of packed red cells. In no instance has there been an increase in the degree of anemia after HN_2. There has been a tendency for the platelet

count to return to normal irrespective of whether it was abnormally high or low prior to therapy. As the total leukocyte count has approached normal levels, the differential has also tended to approach normal, so that in several instances no cells younger than myelocytes have been seen.

Chronic Lymphocyte Leukemia. Fourteen patients with this disease have been treated. Seven are living an average of twelve months after the beginning of therapy with HN_2 and twenty-one months after symptoms appeared. Three patients have been under treatment for more than a year, one for thirty-three months. Seven patients died an average of three and eight-tenths months after HN_2 was first used and thirty-eight months after the appearance of symptoms.

The response of five patients is considered *good.* None of these had received any previous therapy; all are living, working, and asymptomatic. The other nine patients have had very transient benefit or none at all and their responses have been classified as *poor.* Of those who responded well, one had thrombocytopenia and another a marked anemia. These manifestations became less pronounced as the general condition of the patient improved. The remaining three patients had only minor symptoms. Of the nine who did not show a good response, three had received roentgen-ray therapy, which had become ineffective at the time HN_2 was begun, and one had received Fowler's solution without response. Eight of these patients had marked anemia and three, thrombocytopenia. All but two were quite ill at the beginning of treatment. Although we were able to reduce the total leukocyte count, the downward course of the illness was not influenced to any extent. The marked sensitivity of the hemopoietic system of one patient with chronic lymphocytic leukemia (case 101) is illustrated in Fig. 6. Because of the precipitous fall in the erythrocyte, leukocyte, and platelet counts in this case, we have since given, to patients with chronic lymphocytic leukemia, courses of 0.2 mg. per Kg. repeated at intervals of two weeks until the maximum therapeutic effect has been obtained.

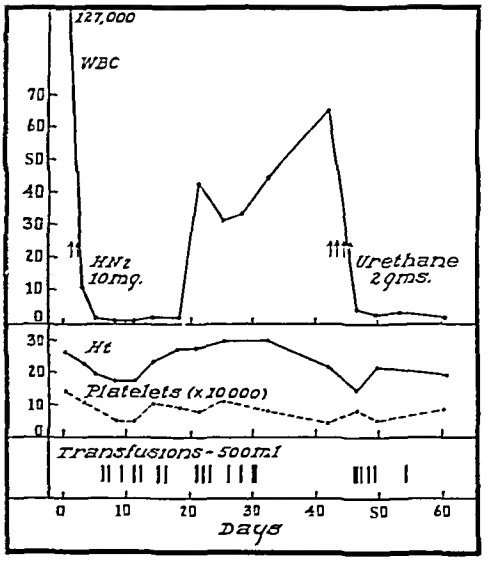

FIG. 6. *Course of a patient with chronic lymphocytic leukemia (case 101).*

Acute Leukemia. Seven patients with myeloblastic, three with lymphoblastic, and two with monocytic leukemia have been treated. All are dead. The average length of life was one and a half months after initiation of therapy, and four months after the onset of symptoms. None had had previous therapy.

One of these patients (case 17) showed a *fair* response because of the marked relief of bone pain during the three months she lived after HN_2 was first used. This patient, as well as another (case 12), improved sufficiently to go home for a short period.

Another patient (case 36) experienced marked though very temporary relief of bone pain.

In one patient (case 43) a rapidly progressive course seemed to be slowed so that the patient lived for three and a half months after treatment was started.

Temporary symptomatic improvement was observed in several others.

A reduction in the total leukocyte count without a significant change in the differential count was observed in all except one (case 54) of the patients with leukocytosis.

Miscellaneous Diseases. Seventeen patients with various disorders have been treated with nitrogen mustard (Table 9). All but five had a *poor* response.

In case 57, in which there was jaundice and extensive skin and subcutaneous metastases from carcinoma of the pancreas,

far reported had previously received roentgen-ray therapy, and in a large proportion of these, the disease had become "resistant" to the effects of irradiation. It is significant that good responses, sometimes for many months, have been seen in many of this group of patients. In our experience the reverse has not been true; in every case in which HN2 no longer produced a remission, subsequent roentgen-ray treatment has also been ineffective.

It has been stated[2] that the chemical agent is too toxic and too ineffective for use in the ordinary, relatively early, and regional case. This statement seems to us to require qualification. Although the value of localized roentgen-ray therapy is well established, the difficulty of determining the true extent of Hodgkin's disease in any particular case must be admitted. We have observed striking benefit from HN2 therapy in early cases of Hodgkin's disease, sometimes even when the disease seemed to be sharply localized and roentgen-ray therapy had been ineffective (case 73). Furthermore, the possibility that local roentgen-ray therapy combined with parenteral nitrogen-mustard administration may offer benefit greater than that which can be achieved by the use of either method of treatment alone must be kept in mind and deserves study.

It is becoming clear that nitrogen mustard is especially useful in cases of Hodgkin's disease in which generalization has begun and constitutional symptoms are present. In such cases remission may possibly be produced more rapidly than by roentgen-ray therapy. The drug is also useful in cases in which so much roentgen-ray therapy has been given that one hesitates to use more.

The results of nitrogen-mustard therapy have not been so promising in *lymphosarcoma* or *reticulum-cell sarcoma*. Although Jacobson et al. report good results in four of six patients, Karnofsky et al.[9] did not observe remissions in any of five cases, and of the sixteen patients included in the present report, a good response occurred in only four.

We have been impressed by the effectiveness of HN2 in the treatment of *chronic myelocytic leukemia*, for we have been able to control the symptoms with HN2 in seven of our eleven patients. The four who responded poorly had all received roentgen-ray therapy until it no longer produced remissions. Jacobson et al. report good results in three of seven patients. The unresponsive ones also failed to respond to roentgen-ray therapy. Karnofsky et al.[9] report a poor response in the one patient treated.

Our patients with *chronic lymphocytic leukemia* treated with HN2 have fallen largely into two groups: (1) those who were really not ill and in whom the characteristic blood findings were more or less incidental; and (2) those with marked lymphadenopathy, splenomegaly, thrombocytopenia, and severe anemia. The patients in the first group have responded favorably to the drug and have shown long remissions following treatment. With one exception (case 97), those in the second group have been refractory to HN2 as well as to other therapeutic agents.

HN2 produced only very temporary alterations in the course of the *acute leukemias*. The relief of bone pain, however, has been helpful in making these patients more comfortable.

The other malignant diseases treated with HN2 have been so various that no definite statements can be made. The improvement of an occasional patient with inoperable carcinoma has been gratifying.

Two disadvantages must be considered in a discussion of the desirability of the nitrogen mustards as therapeutic agents. The first is the nausea and vomiting that almost invariably follow the first injection of each course. These symptoms have varied greatly in intensity and in no patient have we stopped therapy at less than a full course because of this toxic reaction. Several of our patients have preferred roentgen-ray therapy or, in cases of leukemia, urethane therapy. In general, the gastrointestinal symptoms following HN2 administration have not been so long-lasting as those following roentgen-ray therapy.

The second disadvantage is the depressant effect of these agents upon the cellular elements of the blood. Nevertheless, serious leukopenias have been most unusual and no

fatalities have resulted from this cause. When anemia and thrombocytopenia have occurred, they have been short-lived and have not produced serious symptoms. It is noteworthy that in a number of cases, especially in cases of Hodgkin's disease and chronic myelocytic leukemia, anemia due to the disease and existing prior to therapy has been relieved or has entirely disappeared as general improvement took place. This has been less true when, in addition to anemia, leukopenia or thrombocytopenia existed prior to initiation of treatment.

The possibility of cumulative toxicity seems to be of more theoretical than practical interest. There is no evidence that this occurs. Five of our patients have received a total dose of more than 3.0 mg. per Kg. In none of these has an increased hemopoietic-system sensitivity been encountered.

One man (case 11) with chronic myelocytic leukemia has received a total of 6.2 mg. per Kg. (414 mg.) of HN_2 in a period of thirty months. He continues to respond as well as ever, and there is no evidence of cumulative toxicity.

Another patient (case 16) with Hodgkin's disease has received 4.7 mg. per Kg. (266 mg.) in twenty-eight months. She has just recently completed her twelfth course, having been given a dose of 0.6 mg. per Kg., which is as great as any she has received. Mild leukopenia followed this course but this was of no greater degree than on two previous occasions.

The nitrogen mustards that have received clinical trial are only two members of a very large class of compounds. It is hoped that the future may see the development of compounds that are more specific in their effect on malignant tissue and less damaging to the hemopoietic system. The success of the first two agents used certainly encourages this hope.

In comparison to roentgen-rays and radioactive phosphorus (P^{32}), the nitrogen mustards possess the advantage of being available where radiation may not be. They can be administered readily. While the nitrogen mustards are extremely toxic drugs, and dangerous leukopenia and thrombocytopenia can be easily produced, they must be regarded as valuable therapeutic agents in the hands of the physician who is supported by an efficient laboratory.

Summary

1. The effects of methyl-bis (β-chloroethyl) amine hydrochloride (nitrogen mustard) in 102 patients — 32 with Hodgkin's disease, 11 with lymphosarcoma, 5 with reticulum-cell sarcoma, 37 with leukemia, and 17 with miscellaneous disorders — are described.

2. A marked palliative effect upon adenopathy, fever, bone pain, splenomegaly, and various other clinical symptoms has been observed in many patients with Hodgkin's disease, lymphosarcoma, and leukemia.

3. Nitrogen mustard has produced remissions in a number of patients with Hodgkin's disease who were considered to be "roentgen-ray resistant."

4. Toxic manifestations of nausea and vomiting were observed in most patients following nitrogen-mustard administration, but the intensity of these symptoms varied greatly.

5. Nitrogen-mustard therapy very frequently resulted in a decrease in leukocyte count with lymphocytopenia and granulocytopenia. This was often accompanied by a variable decrease in red cells and a decrease in platelets, but in no patient did serious complications arise as the result of these effects.

6. Following the initial decrease in blood elements, an increase in red cells, even to complete disappearance of anemia and of thrombocytopenia, resulted in those patients responding favorably. In leukemia, a fall in the leukocyte count was often followed by a decrease in anemia or its complete disappearance.

7. Ultimately nitrogen-mustard therapy, like irradiation, proved ineffective.

8. Ease of administration, availability in communities where irradiation may not be obtainable, effectiveness in some "roentgen-ray resistant" cases and, rarely, a better tolerance for nitrogen mustard, are advantages of nitrogen mustard as compared with roentgen-ray therapy.

TABLE 1

DATA CONCERNING PATIENTS TREATED WITH NITROGEN MUSTARD

Diagnosis	*Cases*	*Sex*		*Age range (years)*	*Duration symptoms before HN2 (months)**		*Number previously treated, x-rays*	*Number "resistant," x-rays*
		M	*F*					
Hodgkin's disease	32	19	13	14-67	3-60	(22)	26	13
Lymphosarcoma	11	7	4	39-72	1-69	(26)	9	3
Reticulum-cell sarcoma	5	1	4	11-82	1-14	(7½)	2	2
Chronic myelocytic leukemia	11	7	4	12-58	3-52	(25)	5	4
Chronic lymphocytic leukemia	14	12	2	41-87	1-121	(22)	3	2
Acute leukemia	12	7	5	3-65	1/3-10	(2½)	0	0

* Numbers in parentheses denote the average.

TABLE 2

RESULTS OF THERAPY

Diagnosis	*No. of cases*	*Total dose mg. (mg./Kg.)*	*Results (per cent)*			*Patients living*		*Patients dead*		*Patients dead Duration of symptoms, months**
			good	*fair*	*poor*	*No.*	*Time since 1st HN2, months**	*No.*	*Time, 1st HN2 to death**	
Hodgkin's disease	32	24-266 (0.6-4.7)	17 (53)	5 (16)	10 (31)	13	6-33 (15)	19	1/3-28 (8)	15-79 (32)
Lymphosarcoma	11	14-120 (0.35-2.0)	3 (27)	1 (9)	7 (64)	3	4-13 (9)	9	2-12 (5)	9-72½ (34)
Reticulum-cell sarcoma	5	4-48 (0.06-1.2)	1 (20)	0	4 (80)	0		5	¾-10 (3½)	4½-14½ (11)
Chronic myelocytic leukemia	11	33.6-413.5 (0.7-6.2)	7 (64)	1 (9)	3 (27)	7	5½-30 (16)	4	1-4½ (3)	37-53 (47)
Chronic lymphocytic Leukemia	14	16.5-125 (0.2-1.3)	5 (36)	0	9 (64)	7	3-33 (12)	7	½-10 (4)	1½-131 (38)
Acute leukemia	12	5.6-63.5 (0.3-3.7)	0	1 (8)	11 (92)	0		12	½-3½ (1½)	2-10½ (4)

* Numbers in parentheses denote the average.

TABLE 3

HODGKIN'S DISEASE

No.	Sex and age	Duration prior to HN_2 (mos.)	Previous therapy	Effect	Condition prior to HN_2*	No. of courses	Total dose mg.(mg./Kg.)	Early effect	Other therapy	Time since 1st HN_2 (mos.)	Present condition and comment	Final evaluation
1 M.P.	F 27	19	X-rays 7 mos.	Poor	Very poor anemia lung	11	192.8(4.0)	Good	X-rays 2 courses	12	Dead	Good
2 W.R.	M 57	24	X-rays 24 mos.	Good	Poor anemia leukopenia thrombopenia	4	109.9(1.8)	Poor	....	7	Dead	Poor
3 F.H.	M 40	36	X-rays 24 mos.	Good	Moribund spine	1	24.0(0.6)	Poor	....	¼	Dead	Poor
4 N.S.	F 26	60	X-rays 15 mos.	Poor	Poor anemia	7	110.3(2.4)	Good	....	9	Dead; felt well for 7 mos.	Good
6 A.B.	M 32	4	X-rays 3 mos.	Fair	Fair cerebellar signs	2	73.2(1.0)	Good	....	33	Living; 26 mos. remission after 1st course	Good
8 M.C.	F 53	55	X-rays 4 yrs.	Good	Fair mediastinum	2	70.2(1.1)	Good	X-rays 3 courses	24	Dead	Good
15 F.T.	F 28	8	X-rays 3 mos.	Poor	Poor anemia leukopenia thrombopenia fever	3	50.0(1.0)	Poor	....	2	Dead; fever reduced to normal	Good
16 H.S.	F 21	6	None	....	Poor lung abscess	11	266.0(4.7)	Good	X-rays 9 courses	29	Dead; x-rays and HN_2 equally effective	Good
18 A.S.	M 33	12	X-rays 6 mos.	Poor	Poor mediastinum lung	8	168.0(2.8)	Good	X-rays 2 courses	16	Dead; best results from x-rays + HN_2	Good
19 R.H.	M 34	24	X-rays 17 mos.	Fair	Good chest pain	3	86.5(1.1)	Fair	X-rays	11	Dead	Fair
23 E.C.	F 67	9	None	....	Poor spine	2	67.0(1.2)	Good	....	6	Dead; marked relief of back & abdominal pain	Fair

* Only the chief sites of involvement are indicated.

TABLE 3 (*Continued*)

No.	Sex and age	Duration prior to HN2 (mos.)	Previous therapy	Effect	Condition prior to HN2*	No. of courses	Total dose mg. (mg./Kg.)	Early effect	Other therapy	Time since 1st HN2 (mos.)	Present condition and comment	Final evaluation
24 E.R.	M 26	37	X-rays 2 courses	Good	Fair anemia fever mediastinum	1	42.0 (0.6)	Poor	....	3	Dead; relief of fever	Poor
27 J.M.	M 22	36	X-rays 3 courses splenectomy	Good	Good fever leukopenia	7	130.0 (1.9)	Good	X-rays 2 courses	23	Living; recurrent fever	Good
28 B.T.	F 20	14	X-rays 1 yr.	Initially good; later poor	Poor anemia mediastinum lung	1	24.0 (0.6)	Poor	X-rays 2 courses	3	Dead; Hodgkin's sarcoma	Poor
33 T.G.	M 46	3	None	....	Good adenopathy	8	202.5 (3.2)	Good	....	22	Living; excellent condition	Good
40 C.W.	M 24	17	X-rays 16 mos.	Poor	Poor anemia leukopenia lung	4	62.0 (1.2)	Poor	....	3	Dead; Hodgkin's sarcoma	Poor
41 E.Y.	M 61	31	X-rays 7 mos.	Fair	Fair fever anemia	4	60.0 (1.0)	Fair	X-rays	5	Dead; relief of fever	Fair
42 H.J.	M 65	11	X-rays just prior to HN2	....	Fair weakness adenopathy	3	69.0 (1.3)	Good	....	15	Living; excellent condition; x-rays + HN2 seemed especially good	Good
47 M.D.S.	M 41	32	X-rays 2 courses	Good	Good adenopathy	2	56.0 (0.8)	Good	....	14	Living; asymptomatic	Good
50 M.H.	F 47	11	None	....	Poor fever cachexia adenopathy	6	105.5 (2.7)	Fair	X-rays	7	Dead; relieved fever & adenopathy	Fair
52 J.D.	F 14	5	X-rays 2 courses	Poor	Poor anemia lung mediastinum	4	77.8 (2.2)	Good	....	13	Living	Good

TABLE 3 (*Continued*)

No.	Sex and age	Duration prior to HN2(mos.)	Previous therapy	Effect	Condition prior to HN2*	No. of courses	Total dose mg.(mg./Kg.)	Early effect	Other therapy	Time since 1st HN2(mos.)	Present condition and comment	Final evaluation
55 E.G.	M 36	55	X-rays 2½ yrs.	Initially good; reached tolerance	Fair mediastinum lung	2	60 0(1.0)	Good	....	12	Living	Fair
61 W.B.	M 28	31	X-rays 2 yrs.	Good	Good adenopathy	2	84.0(1.0)	Good	X-rays 1 course	12	Living; asymptomatic	Good
62 C.B.	M 25	54	X-rays 4 courses	Initially good; later poor	Fair back pain wt. loss anemia	3	66.9(1.1)	Good	X-rays 1 dose	10	Living; working	Good
63 M T.	F 36	15	X-rays 1 yr.	Initially fair; later poor	Poor anemia fever adenopathy	1	25.0(0.5)	Poor	X-rays	3	Dead; Hodgkin's sarcoma	Poor
67 S.P.	F 29	22	X-rays 2 courses	Good	Fair back pain small bowel	4	110.0(1.8)	Good	....	10	Living; asymptomatic	Good
69 G.B.	M 40	6	None	....	Good adenopathy	2	60.0(1.0)	Good	....	10	Living; working	Good
73 H.G.	M 34	12	X-rays 1 course	Fair	Poor spinal block	2	63.0(1.0)	Good	....	10	Living; working 9 mos. since last therapy	Good
81 W.H.	F 32	54	X-rays 4 courses	Initially good; later poor	Poor fever lung	2	76.0(1.3)	Poor	....	5	Dead	Poor
82 F.A.	M 30	15	X-rays 5 courses	Initially good; later poor	Poor fever anemia skin	3	87.0(1.4)	Poor	X-rays 2 courses	2	Dead	Poor
85 E G.	F 38	5	None	....	Fair fever wt. loss adenopathy	3	122.0(1.7)	Good	....	6	Living; asymptomatic	Good
86 J.F.	M 57	5	X-rays 1 course	Poor	Poor anemia fever abdominal masses	1	36.0(0.6)	Poor	....	3½	Dead	Poor

* Only the chief sites of involvement are indicated.

TABLE 4

LYMPHOSARCOMA

No.	Sex and age	Duration prior to HN2 (mos.)	Previous therapy	Effect	Condition prior to HN2*	No. of courses	Total dose mg. (mg./Kg.)	Early effect	Other therapy	Time since 1st HN2 (mos.)	Present condition and comment	Final evaluation
9 L.P.	M 57	36	Surgery x-rays radium 5 mos.	Good	Poor anemia cachexia liver abscess	4	108.1 (2.0)	Good	None	12	Dead; perforated bowel	Good
13 J.T.	M 39	40	None	....	Fair anemia adenopathy; abdominal mass	3 (in 6 weeks)	120.0 (1.9)	Poor	X-rays	4½	Dead	Poor
14 I C.	F 50	24	X-rays 18 mos.	Good	Poor weakness adenopathy abdominal mass	3	60.0 (1.2)	Fair	....	2½	Dead	Poor
21 P.K.	M 56	7	X-rays 2 courses	Good	Fair anemia fever abdominal mass	1	36.0 (0.6)	Poor	....	2	Dead	Poor
25 A.V.	M 62	12	X-rays 2 mos.	Fair	Fair anemia	3	85.0 (1.6)	Fair	....	5	Dead	Poor
39 L.S.	F 39	12	X-rays 1 course	Poor	Poor anemia cachexia abdominal mass	1	20.0 (0.5)	Poor	....	2	Dead	Poor
51 C.W.	F 59	9	None	....	Good adenopathy	1	33.0 (0.6)	Good	....	13	Living; working asymptomatic	Good
65 G.M.	M 60	60	X-rays 6 courses	Good	Good adenopathy splenomegaly	3	70.0 (1.4)	Good	X-rays	11	Dead	Good
84 A.L.	F 39	14	X-rays 5 courses	Initially good; later poor	Poor anemia leukopenia abdominal mass	2	14.0 (0.35)	Poor	....	3	Dead	Poor
87 A.B.	M 49	69	X-rays 5 yrs.	Initially good; later poor	Poor anemia abdominal mass	2	51.0 (0.7)	Poor	....	3½	Dead	Poor
98 C.C.	M 72	1	X-rays	Good	Fair adenopathy large tonsils	3	76.0 (1.0)	Good	X-rays	4	Living; effect short-lived	Fair

* Only the chief sites of involvement are indicated.

TABLE 5

RETICULUM-CELL SARCOMA

No.	Sex and age	Duration prior to HN2 (mos.)	Previous therapy	Effect	Condition prior to HN2*	No. of courses	Total dose mg. (mg./Kg.)	Early effect	Other therapy	Time since 1st HN2 (mos.)	Present condition and comment	Final evaluation
26 I.P.	F 82	3	None	....	Good adenopathy	1	29.0 (0.5)	Good	....	10	Dead; did not return for repeat therapy	Good
30 A.C.	F 11	1	None	....	Fair anemia adenopathy splenomegaly	2	48.0 (1.2)	Poor	X-rays	3½	Dead	Poor
35 E.D.	M 29	12	None	....	Poor anemia leukopenia purpura fever cachexia	1 dose	4.0 (0.06)	Poor	....	1½	Dead; severe toxic reaction to 1 dose	Poor
80 M.G.	F 36	8	X-rays 6 mos.	Initially good; later poor	Poor anemia lung adenopathy splenomegaly hepatomegaly	2	29.0 (0.7)	Poor	....	1½	Dead	Poor
91 A.B.	F 50	14	X-rays 4 mos.	Initially good; later poor	Poor anemia wt. loss	1	17.2 (0.4)	Poor	....	¾	Dead	Poor

* Only the chief sites of involvement are indicated.

TABLE 6

CHRONIC MYELOCYTIC LEUKEMIA

No.	*Sex and age*	*Duration prior to HN2 (mos.)*	*Previous therapy*	*Effect*	*Condition prior to HN2**	*No. of courses*	*Total dose mg. (mg./Kg.)*	*Early effect*	*Other therapy*	*Time since 1st HN2 (mos.)*	*Present condition and comment*	*Final evaluation*
10 F.M.	F 33	36	X-rays 3 yrs.	Initially fair; later poor	Poor anemia thrombopenia fever	1	33.6 (0.7)	Poor	....	1	Dead	Poor
11 B.C.	M 52	52	X-rays 4 courses	Good	Poor anemia wt. loss	Repeated small doses	413.5 (6.2)	Good	....	30	Living working asymptomatic	Good
22 G.W.	F 56	8	None	....	Fair anemia wt. loss	5 (14 mos.)	96.6 (2.0)	Good	Urethane 112 gm. in 12 mos.	26	Living asymptomatic; urethane better than HN2	Good
31 M.M.	F 58	3	None	....	Fair anemia	8	242.5 (3.9)	Good	Urethane 287.5 gm. in 5½ mos.	23	Living working; urethane a failure	Good
44 A.H.	M 35	24	None	....	Poor fever anemia wt. loss	7 (in 6 mos.)	159.0 (2.5)	Good	Urethane 316 gm. in 7 mos.	14	Living working; prefers urethane	Good
56 N.K.	M 39	50	X-rays 3 courses	Initially good; later poor	Poor anemia	4	132.0 (1.9)	Good	....	3	Dead	Fair
74 A.G.	M 28	42	X-rays since onset	Initially good; later poor	Poor anemia marked splenomegaly	1	54.0 (0.6)	Poor	Urethane and X-rays	3	Dead	Poor
78 D.E.	M 51	3	None	....	Poor anemia	Repeated small doses	174.5 (2.8)	Good	None	7	Living working	Good
83 G.B.	M 22	6	None	....	Fair anemia wt. loss	Repeated small doses	120.1 (1.8)	Good	None	6	Living working asymptomatic	Good
88 V.B.	F 52	48	X-rays 4 yrs.; urethane 61 gm.	Initially good; later poor	Poor anemia wt. loss	5	58.5 (1.5)	Poor	X-rays 1 course	4½	Dead	Poor
92 L.B.	M 12	6	None	....	Fair anemia wt. loss	Repeated small doses	80.5 (2.3)	Good	....	5½	Living asymptomatic	Good

* Only the chief sites of involvement are indicated.

No	Sex and age	Duration prior to HN_2 (mos.)	Previous therapy	Effect	Condition prior to HN_2*	No. of courses	Total dose mg (mg./Kg.)	Early effect	Other therapy	Time since 1st HN_2 (mos.)	Present condition and comment	Final evaluation
5 W.G.	M 51	24	None	....	Good, fatigability	5	59.6 (1.0)	Good	....	33	Living, working asymptomatic	Good
7 S.S.	M 87	1	None	....	Poor, anemia thrombopenia	1	38.4 (0.6)	Poor	....	½	Dead no autopsy; cause of death not known	Poor
34 J.S.	M 59	17	None	....	Good	1	30.0 (0.5)	Good	....	22	Living; working	Good
45 E.G.	M 45	6	None	.. .	Good, fatigability	3	125.0 (1.3)	Good	None	1¼	Living, working asymptomatic	Good
53 H.R.	M 56	36	X-rays 2 courses	Fair	Poor, anemia thrombopenia	1	44.0 (0.8)	Poor	None	1	Dead; reduced W.B.C — no other effect	Poor
60 J.C.	F 52	8	X-rays 2 mos	Poor	Poor, anemia fever	1	54.5 (0.8)	Poor	None	7	Dead	Poor
68 L.L.	F 60	121	X-rays 3 yrs	Initially good, later poor	Poor, anemia adenopathy	1	16.5 (0.3)	Poor	X-rays urethane	10	Dead no effect	Poor
70 J.R.	M 67	36	None	....	Poor, anemia thrombopenia wt. loss	1	35.0 (0.5)	Poor	Urethane 5 1.gm	2½	Dead	Poor
76 L.B.	M 64	1¼	Fowler's solution	Poor	Poor, anemia wt. loss	1	40.0 (0.5)	Poor	None	3½	Dead	Poor
93 M.T.	M 44	2½	None	....	Fair; adenopathy	2	48.0 (0.8)	Poor	X-rays	¼	Living	Poor
97 Z.B.	M 58	4	None	....	Poor, marked anemia	1	32.0 (0.4)	Good	....	¼	Living working	Good
101 L.C.	M 51	24	None	....	Poor, marked anemia	1	20.0 (0.2)	Poor	Urethane	2	Dead	Poor
102 L.V.	M 41	6	None	....	Good, adenopathy thrombopenia	1	35.0 (0.5)	Good	....	3	Living asymptomatic	Good
103 A.S.	M 44	3	None	....	Fair; anemia cryoglobulinemia, Raynaud's syndrome	1	26.0 (0.4)	Poor	None	3	Living; no definite effect	Poor

* Only the chief sites of involvement are indicated

TABLE 8

ACUTE LEUKEMIA

No.	Sex and age	Duration prior to HN_2 (mos.)	Previous therapy	Effect	Condition prior to HN_2*	No. of courses	Total dose mg. (mg./Kg.)	Early effect	Other therapy	Time since 1st HN_2 (mos.)	Present condition and comment	Final evaluation
12 J.T.	M 65	1	None	....	Poor *myeloblastic* anemia thrombopenia fever	1	18.0 (0.3)	Poor	....	1½	Dead	Poor
17 M.H.	F 23	3	None	....	Poor *myeloblastic* fever bone pain	3	58.9 (1.2)	Fair	....	3	Dead; considerable relief of pain	Fair
36 E.P.	F 20	2	None	....	Poor *myeloblastic* fever bone pain	4	46.0 (0.9)	Fair	None	2½	Dead; considerable but short-lived relief of pain	Poor
43 R.E.	M 4	10 days	None	....	Poor *myeloblastic* anemia fever	Frequent small doses	63.5 (3.7)	Fair	X-rays 450 r	3½	Dead; apparently stopped rapid progress of disease	Poor
58 G.B.	M 32	10 days	None	....	Poor *myeloblastic* fever lung infiltration	2	32.4 (0.6)	Poor	Urethane 55 gm.	2	Dead; short-lived relief of chest pain	Poor
59 R.G.	M 3	4	None	....	Poor *myeloblastic* anemia purpura fever	1	3.9 (0.3)	Poor	....	½	Dead	Poor
100 D.K.	M 7	2	None	....	Poor *myeloblastic* anemia purpura bone pain fever	1	9.0 (0.5)	Fair	....	½	Dead; relief of fever and alleviation of pain	Poor
46 J.H.	F 3	3	None	....	Poor *lymphoblastic* anemia fever purpura	1	12.9 (1.0)	Poor	None	1¾	Dead; no definite effect	Poor

TABLE 8 (*Continued*)

No.	Sex and age	Duration prior to HN2(mos.)	Previous therapy	Effect	Condition prior to HN2*	No. of courses	Total dose mg.(mg./Kg.)	Early effect	Other therapy	Time since 1st HN2(mos.)	Present condition and comment	Final evaluation
89 H.C.	M 36	2	None	....	Poor *lymphoblastic* anemia purpura	1	28.0(0.35)	Poor	None	1	Dead	Poor
90 G.C.	M 25	2	None	....	Poor *lymphoblastic* purpura	1	24.0(0.3)	Poor	....	1/3	Dead G.I.-hemorrhage	Poor
54 E.N.	F 19	1	None	....	Poor *monocytic* anemia purpura fever	1	21.0(0.4)	Poor	None	1	Dead	Poor
94 K.M.	F 6	10	None	....	Poor *monocytic* anemia purpura fever	1	5.6(0.4)	Poor	None	½	Dead	Poor

* Only the chief sites of involvement are indicated.

TABLE 9
MISCELLANEOUS DISEASES

No.	Diagnosis	Sex and age	Duration prior to HN2 (mos.)	Previous therapy	Effect	Condition prior to HN2*	No. of courses	Total dose mg. (mg./Kg.)	Effect	Other therapy	Time since 1st HN2 (mos.)	Present condition and comment	Final evaluation
20 J.H.	Malignant melanoma	M 44	16	Surgery	Poor	Cachexia widespread metastases	1	36.0(0.6)	None	None	1½	Dead	Poor
29 B.L.	Cancer cervix	F 51	11	Radium x-rays	Poor	Poor anemia lung metastases	1	30.0(0.6)	Poor	None	1½	Dead	Poor
71 G.C.	Cancer ovary	F 22	24	Surgery	Poor	Poor lung metastases	1	36.0(0.6)	Poor	X-rays	2	Dead	Poor
48 J.C.	Cancer adrenal	M 23	13	X-rays 1 course	Poor	Poor fever extensive metastases	1	24.0(0.4)	Poor	None	1½	Dead	Poor
57 J.N.	Cancer pancreas	M 25	4	X-rays	Poor	Poor cachexia extensive metastases jaundice	1	123.2(1.4)	Fair	Urethane x-rays	2½	Dead; marked but temporary regression of metastatic nodules and jaundice	Fair
37 E.A.	Cancer bronchus	M 54	2	None	Poor	Metastases	1	48.0(0.8)	None	None	1	Dead	Poor
95 A.D.	Cancer bronchus	M 57	2	None	Poor	Poor extensive metastases	2	57.0(0.9)	Fair	X-rays	2	Dead; marked improvement for 4 weeks	Fair
104 A.T.	Cancer bronchus	F 45	25	Surgery	Inoperable	Poor	2	51.2(0.9)	Poor	None	3	Dead	Poor
105 J.N.	Cancer bronchus	M 32	4	X-rays 1 course	Poor	Fair pleural fluid	2	65.4(1.0)	Good	None	2½	Living; working	Fair
79 D.H.	Malignant thymoma	M 20	8	None	....	Moribund mediastinal mass	1	10.0(0.15)	Poor	None	8 hrs.	Dead; probably not result of HN2	Poor
72 H.B.	Fibrosarcoma	M 62	58	Surgery	Poor	Poor extensive metastases	1	46.0(0.9)	Poor	None	1	Dead; some relief of pain	Poor
96 G.A.	Fibrosarcoma	M 26	8	X-rays 2 courses	Poor	Fair lung metastases	1	32.5(0.5)	Poor	X-rays	1	Dead	Poor

TABLE 9 (*Continued*)

No.	*Diagnosis*	*Sex and age*	*Duration prior to HN2 (mos.)*	*Previous therapy*	*Effect*	*Condition prior to HN2**	*No. of courses*	*Total dose mg. (mg./Kg.)*	*Effect*	*Other therapy*	*Time since 1st HN2 (mos.)*	*Present condition and comment*	*Final evaluation*
38 W.W.	Multiple myeloma	M 46		X-rays 1 course	Poor	Poor anemia leukopenia spinal block	1	28.0(0.6)	Poor	Stilbestrol stilbamidine	2	Dead	Poor
64 J.T.	Multiple myeloma	F 47	5	None	....	Anemia pathological fractures	1	24.0(0.4)	Fair	None	2	Dead; good relief of pain	Fair
66 H.G.	Kaposi's sarcoma	M 75	30	X-rays	Good	Good lesion localized	1	30.0(0.5)	None	X-rays	10	Living; subsequent x-rays—excellent results	Poor
32 B.H.	Probable Hodgkin's disease	F 51	67	None	....	Fair pleural fluid wt. loss splenomegaly spinal block	1	30.0(0.5)	None	None	2½	Dead; no autopsy. Biopsy material inadequate	Poor
77 F.K.	Possible Hodgkin's disease	M 52	21	X-rays Fowler's solution	Poor	Fair anemia fever wt. loss	2	43.2(0.8)	Fair	None	3	Lost to follow-up; control of fever and subjective improvement	Fair

* Only the chief sites of involvement are indicated.

TABLE 10

INCIDENCE OF ANEMIA, LEUKOPENIA, AND THROMBOCYTOPENIA FOLLOWING HN_2 THERAPY IN PATIENTS IN WHOM THESE CHANGES WERE NOT PRESENT PRIOR TO THERAPY

Dose (mg./Kg.) per course	*Erythrocytes*			*Leukocytes*			*Platelets*		
	Total courses	*Anemia**	*%*	*Total courses*	*Below 4000*	*%*	*Total courses*	*Below 100,000*	*%*
0.1	3	0		4	0		1	0	
0.2	3	1	13	7	3	26	8	1	10
0.3	9	1		16	4		11	1	
0.4	15	7		37	19		32	7	
0.5	7	2		19	10		11	1	
0.6	17	4	39	33	20	58	23	8	25
0.7	1	1		3	3		1	0	
0.8	2	1		4	3		4	1	
0.9	1	0		2	1		1	0	
1.2				1	1		1	1	
Total	58	17	29	126	64	51	93	20	22

* Volume of packed red cells below 40 ml. per 100 ml.

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The Histological Effects of Nitrogen Mustards on Human Tumors and Tissues

SOPHIE SPITZ, M.D.

DURING World War I[11] it was learned that the sulfur and nitrogen mustards, agents considered suitable for use in chemical warfare by virtue of their vesicant action on the skin and mucous membranes, also had toxic effects on other tissues, particularly the hematopoietic system. After a lapse of years, exhaustive experimental investigations conducted during World War II[4, 5, 8] on normal laboratory animals have indicated primarily a rapid destruction of lymphocytes in lymph nodes, spleen, and thymus; reduction in granulocytes; and in addition, cytotoxic effects on epithelial cells of the intestinal mucosa. It was natural that attempts be made to capitalize on these and other[1, 3] experimental data, and, accordingly, the nitrogen mustards have been used for several years in the treatment of patients with a variety of malignant tumors, especially lymphomas and leukemias.

On the basis of the information now accumulated,[7, 14, 16] it has become evident that the various nitrogen mustards investigated thus far have a valuable, although clearly only palliative, effect on human tumors. However, the clinical use of the nitrogen mustards currently available has been sufficiently encouraging to warrant further search for a more effective chemotherapeutic agent with a chemical composition basically similar to those already used.

An intensive histological study both of animal and of human tumors following treatment would seem mandatory to determine the precise sequence of the selective effects, if any, of these agents on neoplastic cells; moreover, it is evident that in any such project, every organ is worthy of close scrutiny for indications of possible influences contributory to the over-all result. Because of the lack, thus far, of such studies on the tumors of experimental animals and because of the limited availability of surgical specimens from human tumors at intervals properly spaced following therapy, this study of postmortem material was undertaken in the hope of uncovering clues on how the beneficial effects are mediated.

MATERIAL

This study was made on a group of cases treated with nitrogen mustards* on which postmortem examinations were performed during a period of about two and one-half years, beginning March, 1945, and ending October, 1947. Fifty-seven fatal cases have been studied: twelve of Hodgkin's disease, sixteen of lymphosarcoma (including eleven cases of reticulum-cell sarcoma), nine of lymphatic leukemia, seven of myelogenous leukemia, and thirteen cases that included a variety of advanced, inoperable, recurrent, or metastatic malignant tumors.

The clinical data on which correlations were made were obtained from the hospital records as well as from the clinical observations by members of the Medical Service of Memorial Hospital under the direction of Dr. Lloyd F. Craver and by members of the Department of Clinical Investigation of the Sloan-Kettering Institute.

In most of these cases other available forms of therapy, including surgery and external irradiation, had been used and found no longer effective. This was particularly true in the miscellaneous group of carcin-

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* Unless otherwise indicated, the cases in this series were treated with methyl-bis (β-chloroethyl) amine (HN_2).

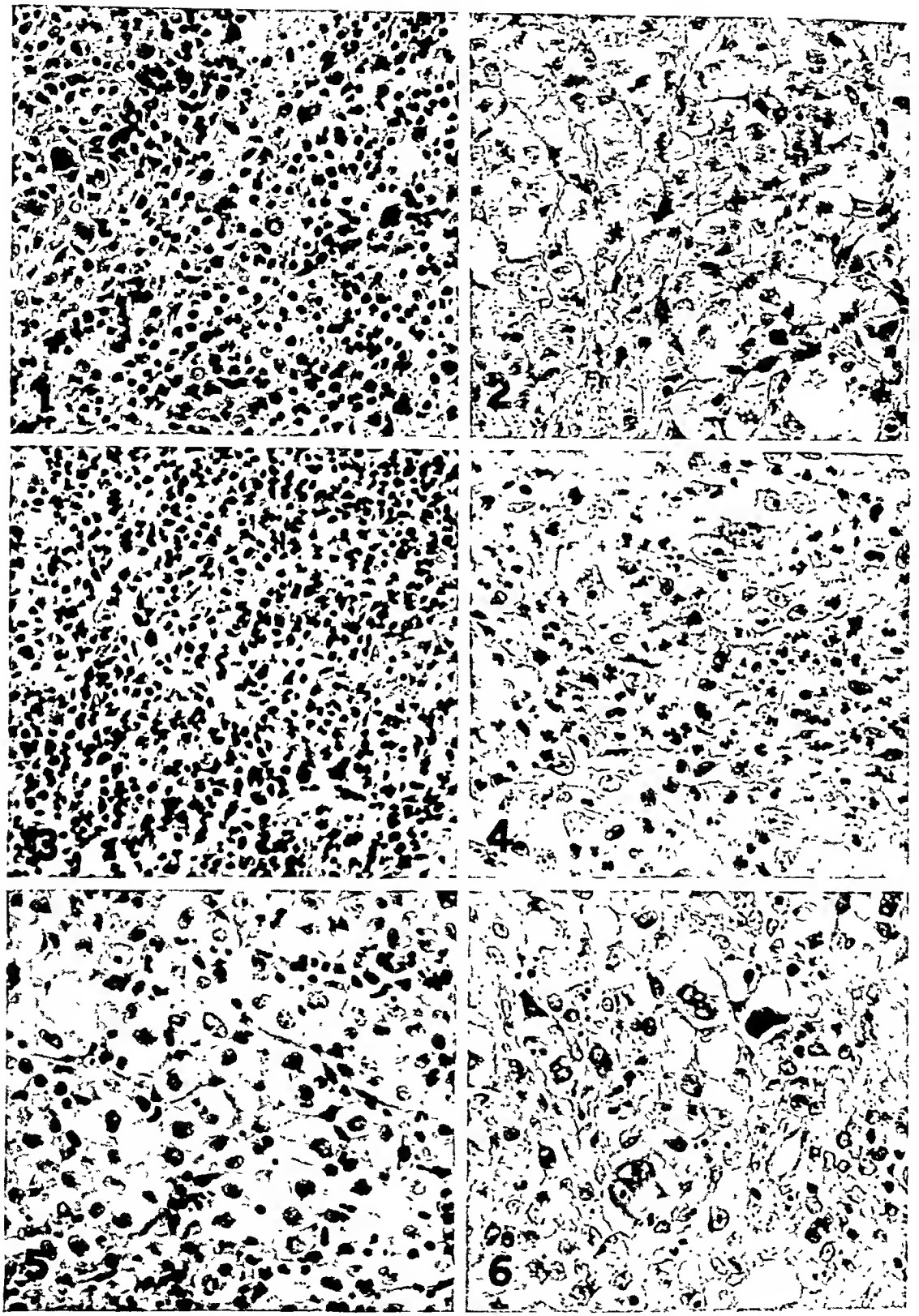

FIG. 1. *For caption see opposite page.*

omas and sarcomas, many of which were inoperable because of extensive metastasis, but it was also true in the lymphomas, of which only one case was treated with nitrogen mustard alone, and in the leukemias of which only six (four children and two adults) were treated with nitrogen mustard to the exclusion of other forms of therapy.

The duration of illness in this group did not differ from the average expected duration of untreated cases. In the group of Hodgkin's disease, the average duration was three years; in lymphosarcoma, three and one-half years; in lymphatic leukemia, three and one-half years (adults); and in myelogenous leukemia, two and one-half years (adults). The average duration in the five children with the diagnosis of acute leukemia was four months.

During their terminal illness, the patients received all forms of supportive therapy including multiple transfusions. Penicillin, streptomycin, and the sulfonamides were also given, since many were, at times, febrile. Almost all patients were purpuric, so that massive intestinal or cerebral hemorrhage formed the most prominent terminal incident.

Complete postmortem examination, excluding the head, was performed in all cases included in this study. An effort was made to do the necropsies as soon after death as possible and, for this reason, autolytic changes were minimal. Permission for the examination of the brain was obtained in so few instances that the material available was not considered worthy of inclusion.

The only selection made of the material available was the exclusion of cases in which irradiation had been so recent or so extensive that it left insufficient material for the study of the uncomplicated mustard effect. Other cases that received radioactive phosphorus were also excluded. Care was taken to delete from study those sections of the tumor taken from areas to which previous irradiation had been administered.

Hematoxylin-eosin preparations of paraffin sections of the tissues were available for study in all cases. In addition, Bielschowsky silver impregnation for reticulum and scarlet-red stains for fat on frozen sections were made on selected cases. Decalcified sections of vertebral marrow taken from the third or fourth lumbar vertebra were studied in all cases, and, in some, the femoral, sternal, and costal marrow as well.

With the exception of a few cases of leukemia, hematoxylin-eosin preparations of paraffin sections of nodes removed surgically for diagnosis were available for study. In most cases these specimens had been removed before the institution of any type of therapy and were used as controls of the original structure of the tumor, although it was acknowledged that with the passage of time the histological structure may have altered to a certain extent even without treatment. In a few instances multiple biopsies made during the course of mustard therapy were also available.

Effect of Nitrogen Mustards on Neoplastic Tissues

Hodgkin's Disease. Of twelve cases of generalized Hodgkin's granuloma, seven had had multiple courses of nitrogen-mustard therapy with the accumulated dosage ranging from 1.2 to 3.5 mg. per Kg. body weight. Three of these had not been treated for five to six months prior to death, primarily because of poor clinical response to the therapy. Four

FIG. 1. *Hodgkin's granuloma. Aspiration biopsy of node before treatment. (× 295.)* FIG. 2. *Hodgkin's granuloma. Same case as Fig. 1, four days after nitrogen-mustard therapy. (× 295.)* FIG. 3. *Hodgkin's granuloma. Aspiration biopsy of node before treatment. (× 295.)* FIG. 4. *Hodgkin's granuloma. Same case as Fig. 3. Three months after initial mustard therapy. Note enlargement of cells. (× 295.)* FIG. 5. *Hodgkin's granuloma. Same case as Figs. 3 and 4. Seven days after nitrogen mustard. Note ballooned cells, disappearance of eosinophils. (× 295.)* FIG. 6. *Hodgkin's granuloma. Same case as Figs. 3, 4 and 5. Two months after the second course of nitrogen mustard and one day after the last dose. Note similar cytoplasmic ballooning in some cells and the striking pleomorphism of the tumor cells. (× 295.)*

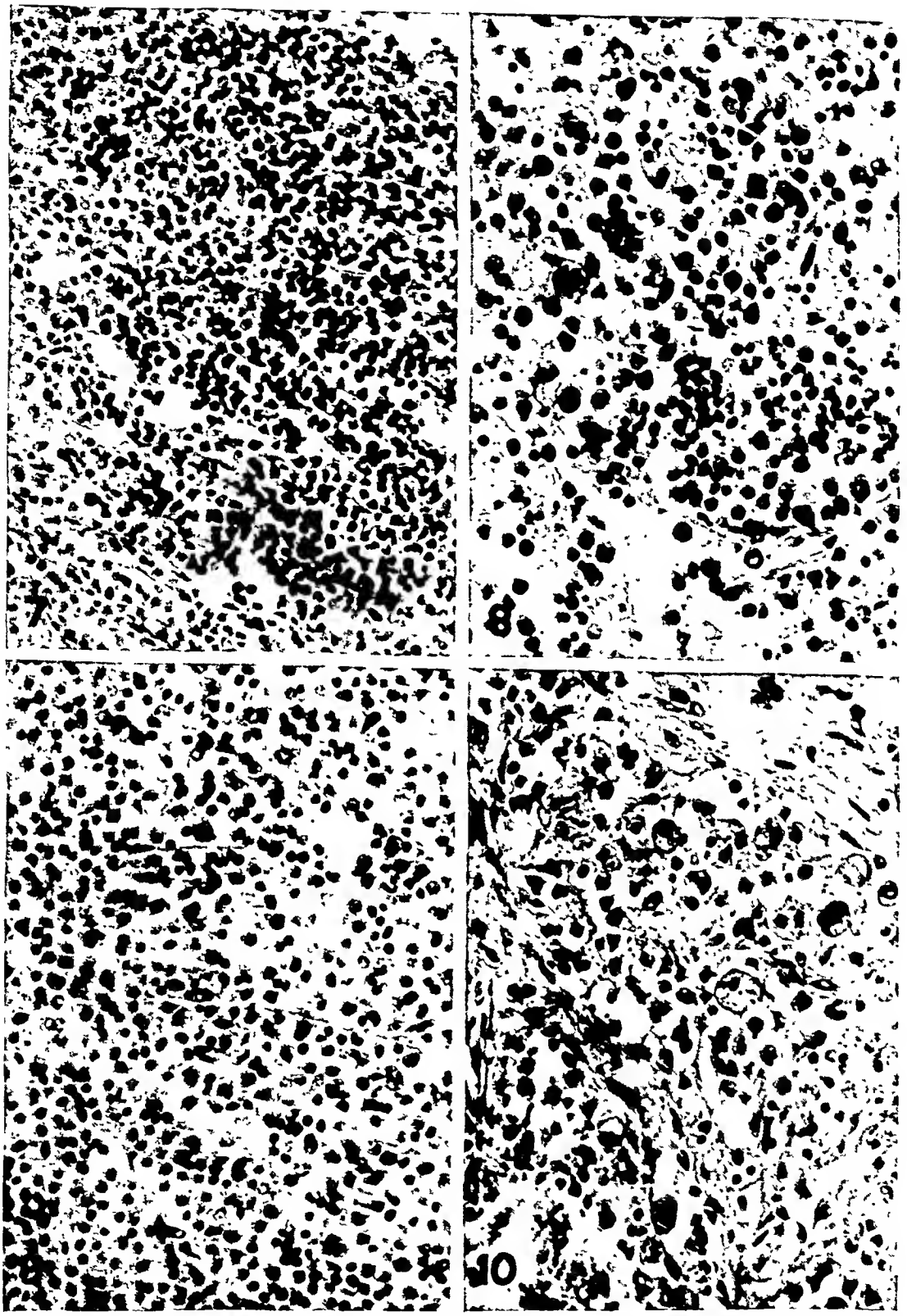

FIG. 7. *Lymphosarcoma. Before treatment. (× 295.)* FIG. 8. *Lymphosarcoma. Same case as Fig. 7. Seventy-two hours after mustard therapy. Note the phagocytosis of fragmented nuclei and the increase in size of residual viable cells. (× 295.)* FIG. 9. *Lymphosarcoma. Before treatment. (× 295.)* FIG. 10. *Lymphosarcoma. Same case as Fig. 9. Seven days after treatment. Note the decrease in number and the increased pleomorphism of the tumor cells some of which have phagocytosed fat. (× 295.)*

others had had their final injection from one to thirty days prior to death. The five remaining cases had received one or two courses of the mustard totaling 0.4 to 0.8 mg. per Kg. body weight from eight to twenty-six days before death.

In five of these twelve, the clinical response to therapy was considered "good" at the time of the first course. But it must be noted that there was no clinical regression of the disease during or after the final course of therapy in any of the cases of this series.

Probably more because of dearth of material than lack of changes, only meager histological evidence of the effect of nitrogen mustards on the cells comprising Hodgkin's disease has been gathered from this postmortem material. There were two cases, however, in which posttreatment surgical material, when compared with pretreatment structure, showed prominent cytological alterations. The original nodes, on which the diagnosis of Hodgkin's disease was based, had been adequately aspirated only a short time before treatment was begun. In the first case, the structure was cellular and numerous Sternberg-Reed cells together with clusters of eosinophils were present (Fig. 1). Neither necrosis nor fibrosis was outstanding. Four days following the first course of mustard therapy, the histological appearance of an excised node was altered to the extent that it was no longer possible to identify confidently any of the cells except the eosinophils (Fig. 2). The remainder of the cells were enlarged, due to ballooned, vacuolated cytoplasm and often swollen nuclei in which the details of chromatin structure could seldom be seen. It was not possible to determine whether these cells represented altered, nonneoplastic reticulum cells or cells of the Sternberg-Reed type. Nevertheless, it was noted that the latter, prominent in the pretreatment node, could not be identified in the tissue only four days following therapy. Mitoses were not numerous; lymphocytes were reduced in number.

In the second case (Fig. 3) the first posttreatment tissue was obtained three months after initial therapy; in this specimen (Fig. 4) the classic histological features of Hodgkin's granuloma were evident. Many cosinophils were present as were scattered Sternberg-Rced cells, but these latter were enlarged because of the presence of cytoplasmic vacuoles. Seven days after the second course of nitrogen mustard another surgically excised node (Fig. 5) revealed no diminution in the number of eosinophils or lymphocytes but did show almost uniform swelling of the other cells in many of which the chromatin details of the nucleus were no longer evident. Mitoses were numerous in these altered cells. Two months following treatment, at postmortem examination, these changes were noted again to some degree, probably because another dose of mustard had been administered one day before death. The most conspicuous change, however, was that the nodes presented a far more pleomorphic appearance than that noted originally (Fig. 6).

Cytological changes were not prominent, in the remaining cases of Hodgkin's disease in which postmortem examination was made from eight to thirty days after treatment. However, apparently independent of the accumulated dosage of mustard and notwithstanding a general reduction in cellularity, there was a definite impression that most of the cells forming the tumor at this stage were larger and more pleomorphic than in the pretreatment sections. Moreover, there was no increase in stroma and no evidence that necrosis occurred as a result of the mustard therapy.

In the three remaining cases, untreated for five to six months prior to death, the histological appearance of nodes removed surgically prior to mustard therapy and that of the postmortem material were practically indistinguishable. Areas of necrosis and fibrosis were present in both, sometimes to even greater extent in the pretreatment tissues. Sternberg-Reed cells were particularly prominent in the postmortem material; eosinophils varied in number whereas lymphocytes seemed somewhat decreased. Vascular lesions, such as swelling of endothelium, thrombosis, or fibrinoid necrosis of the walls of the vessels, were present in both the pretreatment and the posttreatment tissues and

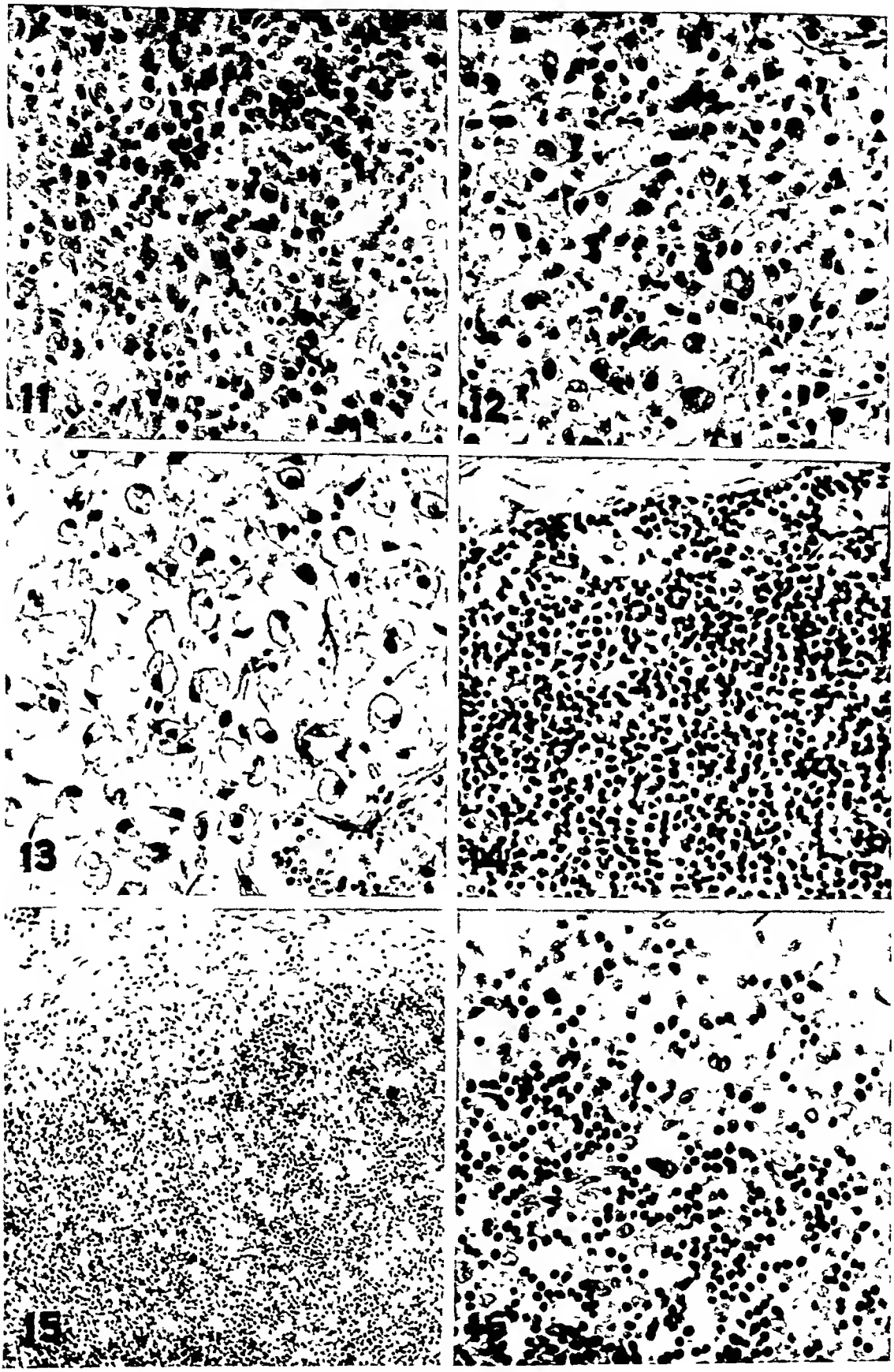

FIG. 11. *For caption see opposite page.*

were not considered relevant to therapy.

Lymphosarcoma. Twelve of the sixteen cases in this group belong to the category of reticulum-cell sarcoma, and four of these were of the pleomorphic giant-cell type. The remainder were classified as the lymphocytic type of lymphosarcoma. All had generalized disease. The dosage of the nitrogen mustards was moderate, consisting of one or two courses totaling 0.4 to 1.2 mg. per Kg. of body weight. The interval from last dose to death ranged from one day to three months. Ten of these cases died within twenty days of the last dose.

The earliest changes were found in a case of reticulum-cell sarcoma after 0.3 mg. per Kg. of body weight had been given over a period beginning seventy-two hours and ending eighteen hours before death. The original tumor (Fig. 7) in this case was compact and quite uniform in structure and cell type; no necrotic areas were noted and mitoses were frequent. In the postmortem sections of nodes there was a definite decrease in the cellularity of the tumor; no longer was there a compact uniform structure but instead, loosely scattered cells separated in places by edema fluid and in others by hemorrhage. Single scattered intact tumor cells were seen among many large macrophages containing from ten to twenty bare, fragmented nuclei (Fig. 8). An occasional pyknotic nucleus was found outside the phagocytes. Earlier phases of nuclear and cytoplasmic deterioration were not evident in the type of preparation used in this study. Other macrophages were not so packed with nuclei but contained erythrocytes, small granules of hemosiderin, and large amounts of fat. In some of these, the nucleus of the macrophage was no longer visible. Although mitoses were not prominent, a few could be found. In some areas destruction of the tumor appeared to be more complete; only the reticular framework of the node and its vessels remained.

With approximately the same dosage (0.4 mg. per Kg.) and similar original histological structure (Fig. 9), there was much less evidence of destruction of the tumor in a case on which postmortem examination was performed eight days after therapy. There was, again, somewhat less cellularity than in the original structure (Fig. 10); bizarre mitoses were common and the sinusoids contained only moderate numbers of macrophages, in the cytoplasm of which were nuclear debris, fat, and blood pigment. An alteration in the cell type was also evident in that tumor giant cells had become noticeably more prominent.

On the other hand, even more conspicuous changes were evident in the tumor nodules in other cases of reticulum-cell sarcoma in which the dosage varied from 0.7 to 1.2 mg. per Kg. and in which death occurred from twelve to twenty-one days following the last mustard injection. The alterations were similar to those described at the early period; in some areas (Fig. 13) they were distinctly more severe although in other foci the neoplastic cells seemed well preserved (Fig. 12). Large numbers of phagocytes either packed with pyknotic nuclei or showing swelling, trabeculation, and vacuolization of the cytoplasm ("blister cells") (Fig. 13) occurred in areas completely devoid of tumor cells. During this period the normal architecture of the nodes again became evident; that is, the sinusoidal structure, previously not visible, was prominent. In addition there were focal areas of necrosis showing irregular peripheral formation of edematous granulation tissue. Mitoses were prominent in the

FIG. 11. *Reticulum-cell sarcoma. Before treatment. (× 295.)* FIG. 12. *Reticulum-cell sarcoma. Same case as Fig. 11. Twenty-one days after treatment. In some areas the tumor is actively growing. (× 295.)* FIG. 13. *Reticulum-cell sarcoma. Same case as Figs. 11 and 12. After treatment. Another area, showing almost complete disappearance of neoplastic cells. (× 295.)* FIG. 14. *Lymphatic leukemia. Node before treatment. Note obliteration of architecture by infiltrate. (× 295.)* FIG. 15. *Lymphatic leukemia. Same case as Fig. 15, seventeen days after mustard therapy. Note unveiling of previously obscured sinusoidal structure. (× 120.)* FIG. 16. *Lymphatic leukemia. Same case as Figs. 14 and 15, after therapy. Residual cells seem unaffected by treatment. (× 295.)*

tumor cells at this stage. One of the cases differed from the remainder in that, twelve days after the last injection, there was fragmentation of the nuclei of almost all tumor cells but only a rare macrophage was found and scanty evidence of phagocytic activity.

In general, after the first twenty-one days and up to two months following treatment, the alterations were evident in steadily decreasing degree. Mitoses became increasingly prominent throughout the period. In the later cases there was far greater pleomorphism of tumor cells and predominance of tumor giant cells as compared with the surgical material. Only occasional macrophages were found and they no longer contained nuclear debris. The fate of the macrophages was not determined in this material.

Four of these tumors were, in the original structure, pleomorphic giant reticulum-cell sarcomas. At the time of autopsy, from one to two months after mustard therapy, little histological change was evident, although clinically there had been "fair" response in two. Since the survival in this group was somewhat longer (thirty to sixty days), it is possible that the interval was too great to indicate the nature of the change causing the regression originally noted clinically.

In the group of lymphosarcomas of predominately lymphocytic-cell type, the alterations in structure were similar to those occurring in lymphatic leukemia.

Lymphatic Leukemia. Nine cases of lymphatic leukemia were studied; five occurred in middle-aged or elderly adults and four in children from 3 to 10 years old. Six of these cases were treated with the newer nitrogen-mustard derivatives, SK 136 and SK 137,[2] but since the histological findings were similar to the two treated with HN_2 they were not considered separately. One patient, who received 0.1 mg. HN_3 per Kg. of body weight, collapsed shortly after the injection and died three days later. This is the only instance of apparent idiosyncrasy or sensitivity in the cases included in this study. In this patient there were no alterations in total peripheral leukocyte count, which was maintained at a level of 300,000 per cu. mm., nor was there reduction in platelet count below 190,000. Moreover, histologically, the extensive visceral leukemic infiltration appeared unaffected at the time of postmortem examination.

Four adults survived from eleven days to twenty-one months after the beginning of mustard therapy (0.34 to 5 mg. per Kg. of body weight) and six to thirty-five days following the last injection. Although the clinical course of the disease in the four children included here was acute and averaged only four months, morphologically the leukemic cells were relatively mature lymphocytes. Clinically the response to nitrogen-mustard therapy in all the children was distinctly better than in the adult group and definite, though short-lived, remissions occurred during the period of therapy. In contrast, remissions occurred in only one of the adults. The four children were treated with several courses each of newer derivatives of nitrogen mustard (SK 136 and SK 137) over periods of two to six months, the total dosage varying from 1.2 to 2.9 mg. per Kg. of body weight. They survived one to thirty days after the last injection. The histological evidences of alteration were similar in both adult and childhood groups.

In five cases, on which postmortem examination was performed from one to thirty-five days following the last treatment, no qualitative changes were noted in the involved tissues. The terminal peripheral leukocyte count in each of these was high; there had been no variation during therapy. The nodes, femoral and vertebral marrow, spleen, liver, and other organs showed diffuse infiltration by unaltered lymphocytes. The structure of nodes was completely masked in the biopsy as well as in the postmortem material.

In four remaining cases, which differed clinically from those showing no morphological alterations only in the reduction of the total leukocyte count during life, there were distinct changes consisting mainly of relative sparsity of cells forming the infiltrate (Figs. 14, 15, 16). The diminution in number of cells was equally evident in all four cases and seemed not to be dependent on total dosage (1.2 to 5 mg.) or on the interval after the last injection (thirteen to thirty-five days).

In addition, it was noted that the fewer lymphocytes there were in nodes the more apparent was a restitution of the previously masked architecture of the node (Fig. 15). The sinuses were cleared of tumor cells and often were crowded with macrophages ("sinus catarrh"). An occasional phagocytic cell contained several pyknotic nuclei and some were "blistered" with fat, but these phenomena were far less striking than in the cases of reticulum-cell sarcoma. The changes were in definite relation to the severity of the leukopenia. Likewise, both the diminution in the leukemic infiltrate in tissues and the leukopenia could be correlated directly with the degree of aplasia of the marrow.

Myelogenous Leukemia. Six cases of myelogenous leukemia, including five adults and one child, were treated with one or more courses of various forms of nitrogen mustards totaling 1.1 to 3.6 mg. per Kg. body weight beginning two weeks to eleven months before death. Of these, three responded fairly well clinically. The remaining three, all cases of chronic myelogenous leukemia, died within one month of the initial treatment. The group responding to therapy was composed of two cases of acute myeloblastic leukemia, one in an adult, the other in the child, and a third case in which the predominating cell during the early phase of the disease was a monocytoid form of early myelocyte. Although most of these cases had high leukocyte counts at the time of death, those patients responding clinically to therapy developed an initial leukopenia more regularly than those in which a remission did not occur. The initial dosage was equivalent in all cases, so that variations in response could not be explained on the basis of variation in dosage.

In four cases, examination of tissues obtained at autopsy yielded no evidence of any effect of the therapy. Three cases of chronic leukemia that had never shown clinical response had been treated with mustard within four to twelve days of death. They presented the expected generalized leukemic infiltrate of the viscera, including liver, spleen, and kidneys. The vertebral marrow was extremely hyperplastic and presented all stages of mature and immature granulocytes as well as scattered megakaryocytes. Erythroblastic foci were present in all. One case of acute leukemia that had responded well to the therapy had not been treated for forty-seven days before death. In this case the marrow was crowded with myeloblasts and relatively few of the more mature granulocytes were present.

The tissues of one child and one adult with acute leukemia showed great reduction of leukemic infiltrate not only in the viscera but in the marrow as well, even though they had been treated as long as twenty-three to thirty-one days before death. The marrow in both was fatty with diffuse edema and a peculiar myxomatous change. Only small islets of cells were present in which were identified a motley of "blasts" and rarely an early erythroblast. Only rare scattered degenerated megakaryocytes were seen. There were also areas of hemorrhage and scattered focal areas of necrosis which were not considered to be autolytic, since many showed proliferation of capillaries and fibroblasts similar to lesions noted in the nodes of the cases of lymphosarcoma.

The spleen showed similar changes; in neither case was there a great increase in weight; small lymphoid follicles were evident although few cells, either lymphocytic or myelocytic, were present in the pulp, which was hemorrhagic. The cords were fibrotic, and the splenic sinusoids dilated but generally empty except for a few pigmented macrophages.

Miscellaneous Malignant Tumors. Thirteen inoperable or recurrent malignant tumors, many of which had extensive metastasis and all of which were in the terminal stages of the disease, were treated with the nitrogen mustards. The total dosage from one or more courses varied from 0.4 to 2.0 mg. per Kg. of body weight. The longest survival time following therapy was six months; the shortest, three days. Surgical biopsy was available for comparative study in all of these cases.

Of this group, there was symptomatic and subjective improvement only in two cases of bronchogenic carcinoma of the anaplastic

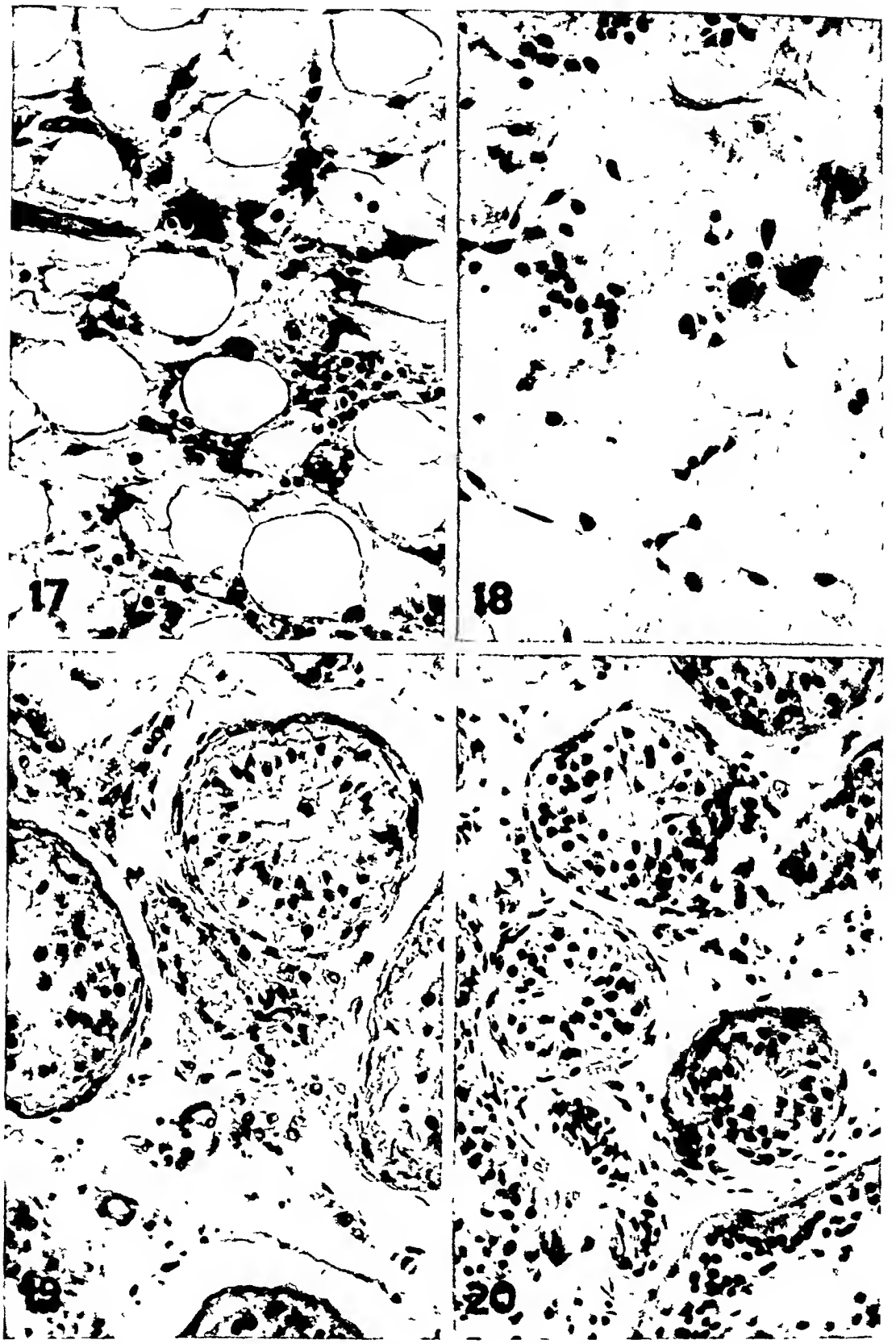

FIG. 17. *Vertebral marrow. Hypoplasia, twenty-one days after nitrogen-mustard therapy. (× 295.)* FIG. 18. *Vertebral marrow. Hypoplasia associated with diffuse myxomatous change, fourteen days after therapy. (× 295.)* FIG. 19. *Testis, age 25 years. Early phase of atrophy, seven days after the beginning of nitrogen-mustard therapy. (× 160.)* FIG. 20. *Testis, age 29 years. Atrophy persisting thirty days after completion of nitrogen-mustard therapy. (× 160.)*

epidermoid type. Although examination of many sections revealed extensive areas of necrosis both in the primary and metastatic foci, comparison with the two cases showing no clinical response, as well as with other similar tumors in untreated patients, particularly in a group in which pneumonectomy had been performed, revealed similar spontaneous necrosis. Neither differences in the extent of the necrosis nor any cytological alterations could be found in the two groups. The same features were characteristic of two retroperitoneal neuroblastomas in children in which necrosis and calcification were common.

The remainder of the cancers that had been treated with nitrogen mustard, including gelatinous adenocarcinoma of the stomach and one of the trachea, malignant melanoma, embryonal adenocarcinoma of the testis, adenocarcinoma of uterus and ovary, and a malignant teratoma of the mediastinum, showed no histological evidence of therapeutic damage. There were no unusual necrotic foci beyond those usually found in bulky tumors, no cytological differences as compared with surgical biopsy material, and no depression of mitotic activity regardless of dosage or interval from therapy to time of death.

Effect of Nitrogen Mustards on Other Tissues

Bone Marrow. Sections of vertebral marrow were available for study in each of the fifty-seven cases in this study. In a number of cases femoral, sternal, and costal marrow sections were also included. Of this material, twenty-two cases were considered suitable for the evaluation of the effects of mustard therapy on previously normal marrow. The remainder were discarded because of the presence of neoplasm locally, since marrow in the vicinity of tumor nodules was often altered even without therapy. None of the cases of leukemia was included in this evaluation.

In seven of the twenty-two the marrow showed no deviation from the normal. Three had received 0.4 to 0.8 mg. per Kg. of body weight within three days before death. Clinically there had been no alterations in the peripheral blood during this period. The marrow cells in these cases were well preserved and showed no definitive nuclear or cytoplasmic alterations. Four cases had received total dosage of mustard varying from 0.4 to 0.8 mg. per Kg. of body weight, but the final injection had been administered thirty to sixty days prior to death. In these last four mentioned cases there had been a transient period of leukopenia and thrombocytopenia following therapy, but peripheral leukocyte counts had risen before death.

The marrow of fifteen cases showed moderate to severe grades of hypoplasia. Moderate hypoplastic changes were observed with dosages of 0.2, 0.4 and 0.8 mg. per Kg. when death ensued twenty-one to forty-five days after treatment. Severe hypoplasia and, in several instances, almost complete aplasia were noted after total dosages of 0.5 to 2.8 mg. per Kg. body weight when the last course (0.4 mg. per Kg.) had been administered from five to thirty days prior to death. The progressive hypoplasia seemed proportional to the size of total dosage of the mustard, and to the rapidity with which multiple courses had been repeated. Only two of the cases so affected had received single courses of mustard therapy of 0.5 and 0.6 mg. per Kg. each at an interval of eight days prior to death; these showed hypoplasia comparable to those studied with greater dosage and at longer intervals. The hypoplasia of the marrow could be correlated positively with the degree of leukopenia and thrombocytopenia that had existed prior to death. The range of the total leukocyte count was from 250 to 2200 cells per cu. mm. and platelet counts ranged from 14,000 to 38,000. As mentioned previously all these cases had purpuric manifestations clinically and on postmorten examination. On the other hand, several in which the marrow appeared histologically unaltered at postmortem examination also had leukopenia and thrombocytopenia during life almost to the same extent as those in the hypoplastic group. The hemoglobin in all cases, whether with normal or hypoplastic marrow, was only moderately reduced but this fact was considered irrelevant, since all cases had received

multiple transfusions during their terminal illness.

Histologically the alterations in three of these cases were moderate and consisted primarily of reduction in the granulocytic cells. Only rarely could a mature polymorphonuclear neutrophil or eosinophil be identified. Very small clusters of fifteen to twenty myelocytes were scattered at wide intervals in the marrow but no differentiation of these cells into segmented neutrophils was noted. The erythroblastic foci in these three cases appeared not to be abnormal either in distribution, number, or appearance of the cells. Megakaryocytes appeared not to be reduced in number although these cells did show structural variations not noted in control cases. There was variation in size and particularly in contour; the cells were most often small, round, or oval, with sharp cytoplasmic membranes. The cytoplasm was more often glassy than vacuolated. The interpretation of these changes was considered equivocal particularly in view of the absence of degenerative phenomena in other cells present. There were manifestations of purpura in the marrow as well as in the viscera. The fat cells were prominent and were separated by erythrocytes. Numerous pigmented phagocytes were present and these were considered a part of the general hemosiderosis resulting from multiple transfusions.

In twelve cases, the changes were extreme and there was almost complete aplasia. The fat cells were sharply defined and almost seemed to be floating in an edematous matrix (Fig. 17). In several instances even the fat cells had almost disappeared and the entire marrow was replaced by a myxomatous, gelatinous substance containing a few cells resembling chondrocytes (Fig. 18).

The progressive changes in cellular elements consisted of complete disappearance of mature granulocytes and myelocytes and gradual diminution in erythroblasts. In the most severe cases there were only a few small cordlike groups of erythroblasts about vessels. In no case was there complete disappearance of erythroblasts. Occasional megakaryocytes were found in all cases although these were greatly reduced in number and altered in appearance. In most of these cases a few plasma cells and reticulum cells were present.

The appearance in these marrows then was one of diffuse edema with patchy or diffuse myxomatous changes in which widely scattered small erythroblastic cords, occasional plasma cells, and rare megakaryocytes were present. The vessels were prominent and were engorged but no necrosis or thrombosis was noted.

Spleen. Excluding all cases of leukemia, there were twelve cases in which the spleen was not involved in the neoplastic process and could therefore be used to evaluate mustard effect on the relatively normal spleen.

Alterations in malpighian follicles constituted one of the most prominent features of the effect. In three cases follicles could not be identified in the sections studied. The central artery was bare and the surrounding tissue not only devoid of lymphocytes but necrotic as well. Fragments of nuclear debris were scattered about the artery in a network of fibrin. There was a moderate degree of fibrosis of the cords and distention of sinusoids. The sinusoids in these cases were usually empty or contained small amounts of protein and a few pigmented macrophages. In addition, there were also focal necroses of the red pulp similar to but apparently not related to follicular necrosis.

These changes occurred in cases in which the entire course of 0.5 to 0.8 mg. per Kg. of body weight had been administered within a period of seven to eight days prior to death. They were not found in cases in which similar or even larger amounts of mustard were delivered within eleven to twenty-one days prior to death or in three cases in which 0.4 mg. per Kg. had been given one to three days before death.

In several cases in which the final course of mustard had been given eleven to twenty-one days before death, there was a general reduction in lymphoid tissue throughout the spleen including follicles and pulp but no attempt was made to obtain quantitative data.

It was seldom that lymph nodes which

had not been involved by tumor were available for study. In several that were secured, the lymphoid cells were sparse, the reticular structure prominent, and the sinusoids very large and distended by macrophages.

Liver. The liver was frequently involved in the lymphomatous disease or by the metastasis of other malignant tumors. In addition, all cases showed varying degrees of hemosiderosis usually associated with multiple transfusions given over protracted periods. Diffuse edema was also noted in many instances and, in these, no alteration of Disse's membrane was detected. These and other changes present in sections of liver were not considered specific.

Adrenal. Sections of adrenal glands were available for study in all cases. Excluding the two neuroblastomas and three cases of bronchogenic carcinoma in which the adrenals contained tumor nodules, there was no enlargement of the gland. Only nine of the fifty-two showed edema of the cortex associated with focal degeneration of cells of the fascicular zone. This alteration did not seem to be related either to the interval following the last administration of mustard or to the size of the accumulated dose.

The lipoid content of the adrenal cortex appeared to be at least normal, or occasionally increased, in forty-four of the fifty-two cases. In only seven were the cells of the zona fasciculata acidophilic and granular; histologically they appeared to contain less than the usual amount of lipoid. This finding occurred in the cases that had had a final injection of mustard from three to thirty days before death.

Testis. Sections of uninvolved testes of thirty males, ranging from 16 to 60 years, and averaging 43 years of age, were available for study. Of these only three (10 per cent) showed active spermiogenesis; the remainder were atrophic. The changes (Fig. 20) consisted of decrease in size of the tubules, occasionally thickening of the basement membrane, and complete absence of spermatocytes and spermatids. The tubules were lined with Sertoli cells alone in most instances but in a few cases a rare spermatogonium was seen (Fig. 19). None of the cases showed more than an occasional completely hyalinized tubule. In no case was there residual evidence of an alteration of the cells in situ.

The three testes showing active spermiogenesis occurred in males 31, 48, and 51 years of age, in two of whom the last injection of mustard had been given one month before death and in one, three days before death. The cases showing atrophy covered the entire range of age, dosage, and intervals of therapy herein included.

Similar studies of the uterus and ovaries could not be carried out, since only five cases were in women less than 45 years of age. Four were cases of leukemia and all showed leukemic infiltrate of the endometrium and purpuric manifestations in the ovaries.

Kidney. In five cases, the glomeruli were enlarged and ischemic. The endothelial cells were swollen and the basement membranes of the glomerular capillaries thickened. In two of these the cells of both layers of Bowman's capsule were swollen and occasionally one layer was adherent to the other. In these last cases the lesion was considered as a true acute diffuse glomerulonephritis although no referable clinical data were available. The renal lesions noted did not include architectural distortion and were of a type and degree that were considered reversible.

In addition, other lesions, such as hydropic vacuolization of the convoluted tubular epithelium and scattered pigmented (hemoglobin) casts in distal tubules, occurred occasionally. Because of their inconstancy these were thought to be related to therapeutic measures other than mustard therapy.

Gastrointestinal Tract. Random sections of stomach, and small and large intestine were available for study in almost every case. No unusual alterations were noted in the epithelial cells of the mucosa of any part of the tract regardless of amount or duration of therapy. Occasionally, there was an impression that lymphoid follicles in the lower portion of the ileum and in the colon were reduced in size, but this impression was not positive enough to be considered trustworthy. Throughout the tract there was frequent evidence of purpura.

COMMENT

Effect of Nitrogen Mustards on Neoplastic Tissues. The most encouraging clinical results have been obtained in the relief of subjective symptoms in Hodgkin's disease, although actual regression of tumor nodules has not always occurred. Cytological changes (Figs. 2, 4, 5), observed particularly in those cases in which tissue was obtained within seven days after therapy, were marked by striking enlargement of reticulum cells and Sternberg-Reed cells principally due to fat. Changes in the nucleus consisted mainly of swelling with loss of chromatin pattern or, occasionally, of pyknosis. Not all cells were equally affected and mitoses in the unaltered cells were apparent even during this destructive phase.

As a part of this study, random sections from other comparative lymph nodes were stained for fat, because a qualitatively similar "blistering" effect had been noted in some of the cells. Sudanophilic droplets were noted in the phagocytes and reticulum cells of hyperplastic nodes, in the neoplastic cells of Hodgkin's disease and lymphosarcoma, both untreated and following roentgen-ray therapy. Except in rare instances, the accumulation of this lipid material following nitrogen-mustard therapy, particularly in reticulum-cell sarcoma, was far greater than under any of the conditions mentioned before. Jaffé[6] noted marked storage of lipids in Hodgkin's granuloma as well as in other lesions following roentgen-ray therapy. The laboratory data were inadequate for any correlation of this fat, noted histologically, with the lipids of the blood. No correlation was present between the quantity of fat in the neoplastic cells and in the adrenal glands.

The nuclear and cytoplasmic changes were not evident in the cases of Hodgkin's disease after an interval of eight days. In most cases, there was, however, a definite transformation of the tumor into a cellular and more pleomorphic one in which multinucleate giant cells were prominent (Fig. 6); in these instances the histological appearance of the tumor was more like that of giant reticulum-cell sarcoma than of Hodgkin's disease. Moreover, lymphocytes and eosinophils, which disappeared relatively early following therapy, seemed not to have reaccumulated in nearly the same numbers. Neither fibrosis nor necrosis was an integral part of the effect. Changes similar to those occurring in Hodgkin's disease have also been noted in biopsies of a case of mycosis fungoides not included in this study.

Notwithstanding the relatively less striking clinical results obtained in lymphosarcomas as compared with Hodgkin's disease, histological changes were more widespread and of longer duration in the former following even very small dosages of nitrogen mustard. Cytological alterations (Figs. 8, 10, 12, 13) consisting of ballooning of the cytoplasm by fat; and extensive fragmentation of nuclei persisted as long as twenty-one days following therapy. Even after this period large numbers of macrophages remained within the tumor nodules but were never prominent in other sites, such as uninvolved lymph nodes, in the spleen, or in the bone marrow. Throughout the span of tumor destruction there was a steadily decreasing population of tumor cells but, at the same time, there was growth of the unaltered cells as indicated by easily demonstrable mitoses and an increasing pleomorphism of the residual cells of the tumor (Fig. 12). These changes are comparable to those described in normal embryonic tissues after exposure to nitrogen mustard.[3]

Cytological alterations were not seen in chronic lymphatic leukemia or in lymphosarcoma of the lymphocytic type. There seemed simply to be a reduction in the number of cells comprising the leukemic infiltrate, restricted to those cases in which the peripheral blood count had been lowered. This finding was limited to the nodes and spleen; it was not possible to evaluate variations in the intensity of the leukemic infiltrate in other organs. As a result of this phenomenon, there was, in some of the lymph nodes, a striking unveiling of the normal architecture previously obscured by lymphocytic infiltration.

Only the acute cases in the group of myelogenous leukemias appeared at all affected by mustard therapy. In these, the diagnosis

could hardly have been made on the basis of the cells remaining in the marrow.

Bone Marrow. The degree of hypoplasia of the bone marrow seemed dependent both on the total accumulated dosage and the interval following therapy. After moderate dosages in some cases, recovery from changes that had begun after an interval of three days were evident as long as thirty to sixty days after the end of therapy. Following multiple courses of nitrogen mustards almost every case showed rather extreme hypoplasia.

There was a consistent reduction in mature and immature granulocytes and in some instances these cells had disappeared altogether. In the more severe grades of hypoplasia, erythroblastic foci were reduced in number and size. Regardless of the severity of the hypoplasia, however, a few erythroblasts could always be found. Megakaryocytes, although showing some equivocal changes, also persisted in small numbers. In addition to hemorrhage, edema and diffuse myxomatous changes were prominent in the more severe degrees of hypoplasia.

These changes in the marrow are in essential agreement with those noted clinically[15] and experimentally[8] but are in contrast to observations on animals following exposure to roentgen rays[9] in which normoblasts disappear from the marrow first. Fibrosis of the marrow, such as that following the administration of radioactive phosphorous,[13] did not occur. The diffuse edema, often with myxomatous changes, has been described following roentgen-ray radiation[9] and in other conditions characterized by exhaustion of the marrow. It has been considered here as a form of serous atrophy of fat, probably related to malnutrition.

Adrenal Glands. Because of an increasing awareness of the adrenal-cortex control of the basic activities of lymphocytes, including their destruction and the release of immune bodies, it is pertinent to note that no unusual morphological alteration occurred in the adrenal glands in this group of cases. In no instance was there enlargement of the adrenal, in contrast to reports in experimental animals,[5] nor in any significant number was the lipoid content noticeably decreased. Chemical analyses of the adrenal of the rat[10] and studies on antibody production in goats[12] have revealed that the destruction of lymphocytes following the administration of nitrogen mustards is due to direct action independent of the adrenal cortex. Changes noted in the adrenal glands experimentally[5] and in this series were attributed to terminal infection and shock rather than to the effect of the mustard.

Testis. It appeared possible that mustard therapy had an effect on spermiogenesis, since 90 per cent of this group showed moderately advanced testicular atrophy, recovery from which seldom occurred. There was at least partial confirmation of this assumption from an analysis of the degree of testicular atrophy occurring in a group of malignant tumors not treated with nitrogen mustard. In forty cases, averaging 46 years of age, with miscellaneous malignant tumors, treated by a variety of methods, atrophy occurred in only fifteen (38 per cent) while twenty-five (62 per cent) showed normal spermiogenesis. Also, in a group of thirty lymphomas and leukemias not treated by mustard but by other standard methods, varying from 19 to 60 years (average age, 36 years), sixteen (57 per cent) were atrophic and thirteen (43 per cent) showed active spermiogenesis. Whereas in cases of malignant lymphomas, testicular atrophy seems to occur with greater frequency than in other malignant tumors, there appears to be a tendency toward greater incidence of atrophy in the cases having had mustard therapy.

Summary and Conclusions

1. The postmortem tissues of fifty-seven cases, consisting of a variety of lymphomas, leukemias, and other malignant tumors, treated with the nitrogen mustards were analyzed histologically.

2. Cytological changes were noted particularly in Hodgkin's disease and in reticulum-cell sarcoma and were attributed to a direct effect of the nitrogen mustard rather than to alterations that may occur spontaneously in lymphomatous diseases.

3. Not all cells were equally affected and some appeared to be spared the injury alto-

gether. With recovery from the initial mustard effect, many of the tumors appeared more pleomorphic than before treatment.

4. No cytological effect was noted in a variety of malignant epithelial tumors.

5. Attributable to the mustard therapy, there was a consistent, apparently cumulative hypoplasia of bone marrow that was associated with the disappearance of the granulocytes and the persistence of small numbers of erythroblasts and megakaryocytes.

6. The effects of nitrogen mustards on human tissues differ from those noted experimentally principally in the absence of demonstrable effect on gastric and intestinal mucosa.

7. Testicular atrophy appeared to occur with greater frequency following nitrogen mustard than with other forms of therapy in control cases.

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STUDIES ON THE CHEMOTHERAPY OF LEUKEMIA

*I. Effect of Certain Nitrogen Mustards and Carbamates on Transmitted Mouse Leukemia**

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A systematic study of a number of chemicals for their power to inhibit the growth of neoplastic tissue has been in progress since 1942 in the laboratories of the Memorial Hospital and of the Sloan-Kettering Institute for Cancer Research.[30]

The program developed and now under way[19] involves the tests of compounds for their effects on normal and neoplastic cells grown in tissue culture by the roller-tube technique, on avian and mammalian tumors grown on the chorioallantoic membrane of the chick embryo, on transplanted and spontaneous solid tumors in mice, and on transplanted mouse leukemia.

A substantial part of the study has involved determinations of the ability of the members of a series of nitrogen mustards (2-chloroethyl amines) to prolong the survival time of mice with transplanted leukemia. Several of these compounds have been found to show definite, although incomplete, therapeutic activity. The results are herewith presented.

During World War II, under the Office of Scientific Research and Development, with the Chemical Warfare Service of the Army, an extensive investigation of the toxicology of the 2-chloroethyl amines was made. The results emphasized the fact, which had been known for some years, that compounds of this type are capable of exerting a profound leukotoxic action. Further knowledge of this effect led naturally to its application to the treatment of neoplastic disorders of hematopoietic tissue. The results have been fully described in the publications of Rhoads,[25] Gilman and Phillips,[12] Goodman, Wintrobe et al.,[13] Jacobson et al.,[17] Karnofsky et al.[20] The reports indicate that at least two and probably three compounds of the nitrogen-mustard group, methyl-bis (2-chloroethyl) amine, tris (2-chloroethyl) amine, and ethyl-bis (2-chloroethyl) amine, have a definite therapeutic value. This finding is in contrast to the results of observations on benzene and allied compounds. Whereas benzene is therapeutically active, its closely related derivatives toluene, xylene, mesitylene, and pseudocumene,[7, 8] are without effect.

Since several members of the group of nitrogen mustards show therapeutic activity and since a large number of compounds can be synthesized with related structures, this series assumes extreme importance as a source of substances potentially useful in the control of neoplasms.

Haddow and Sexton reported in 1946 on the inhibiting effect of ethylcarbamate, ethylphenylcarbamate, and isopropylphenylcarbamate on tumors in mice. Shortly thereafter Paterson, Haddow, ApThomas, and Watkinson reported the beneficial effect of ethylcarbamate in patients with leukemia. More recently the effect of this drug on mouse leukemia has also been studied.[5, 23, 31] At various times, also, benzene,[7, 8, 18, 22] arsenic,[7, 9, 10] the aromatic amines,[1, 2] the diamidines,[19] the steroids,[16, 24] and the colchicine de-

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rivatives[25] have been reported to exert some degree of control on certain types of neoplastic disease. Furthermore, some materials formed in the production of antibiotics have been found to have a preferential inhibitory effect on neoplastic tissue.[6,21] The studies of Roskin,[29] and Hauschka et al.[15] show that *Trypanosoma-cruzi* infection can cause regression of tumors in mice. These reports taken in conjunction with the severe leukopenia frequently seen in patients with visceral leishmaniasis[3] suggested a trial of both live and heat-killed cultures of *Leishmania donovani*.

Methods

Leukemia in man or in the experimental animal provides material of peculiar value to studies of cancer chemotherapy. The constant availability of the neoplastic cell in the circulation makes biopsy a simple procedure, easily repeated at will. The opportunity to obtain neoplastic cells relatively free of stroma is unique. Finally the constant and prolonged course of many forms of the disorder allows the value of several potentially active materials to be reliably compared in a single patient.

Transplanted mouse leukemia was employed because of the work of Flory, Furth and their colleagues.[7,8] They showed that the survival time of mice with this experimental disorder provides a reliable indication of the chemotherapeutic activity of the compounds employed in treatment. The fact that in many respects leukemia in mice simulates the disease in human beings[11] has led to the assumption that compounds therapeutically effective in the mouse may also be active in man.

The mice used in the experiments reported here were of the Akm stock. This line was inbred by Furth from 1928 to 1936 during which period several sublines were established of which Ak was one. A single litter of the Ak line was brought to the Hospital of the Rockefeller Institute for Medical Research in 1936 and was further inbred until 1945 as the RIL line. This was further divided into sublines of which the one described as "b"[26] has been employed in the studies herein reported. Since 1945 this line has been bred by brother and sister matings at the Sloan-Kettering Institute of the Memorial Hospital. The letters Akm designate the particular branch (Memorial) of the original Ak stock. A master colony with brother and sister inbreeding is kept at this Institute. From it a commercial breeder, Carworth Farms, is supplied with sufficient animals to make up twelve breeding colonies. Because the large number of animals necessary for this screening program makes brother and sister inbreeding difficult and costly, the animals at Carworth Farms are bred by pen mating and are used when they reach a weight of approximately 20 gm. During the experiments reported, no decrease in the susceptibility of the animals to the strains of leukemia employed was found in any of the twelve pen-bred colonies. If resistance to leukemia had occurred, the particular colony involved would have been sacrificed and replaced by animals from the inbred master stock.

Two strains of transplanted mouse leukemia were employed. Chloroleukemia Ak 1394[7,8] was obtained from Furth. This was derived from a mouse of the Ak stock that had been irradiated with 235 r at the age of six months. Ten months later the spleen, lymph nodes, and liver were greatly enlarged. All the lymph nodes were light green. The blood-forming organs were heavily infiltrated with myeloblasts and oxidase-positive premyelocytes. The disease as originally transplanted was slowly progressive, although its virulence was somewhat enhanced by successive passages. In the experiments included in this report the animals were usually killed by the leukemia in fifteen to twenty-five days, which indicates a relatively high degree of virulence.

A lymphoid leukemia, Akm 9417, that first developed spontaneously in an eight-months-old male mouse of the Akm strain, was employed. It was manifested by enlarged lymph nodes and spleen and an elevation in the number of leukocytes, most of which were immature lymphocytes. This strain of cells usually killed in twenty to thirty days, although in some experiments deaths were seen as early as the fifteenth day.

To transplant the leukemia, a suspension of the splenic cells of a single leukemic animal was made by mincing the tissue in 15 cc. of sterile Gey's solution and filtering it through cotton. Each of the mice was injected intraperitoneally with 0.1 cc. of the suspension. This volume contained from 500,000 to 8,000,000 cells. The suspension was agitated almost constantly during use. Hence it can be assumed that all mice in a given experiment received approximately the same number of cells. No attempt was made to inject the same number of cells in every experiment. This may in part account for the variations in resistance to therapy shown by the results of different experiments. In future work the number of cells in the inoculum will be kept constant.

The first step in the test of an agent of unknown chemotherapeutic power was the determination of the maximum tolerated dose.* Compounds sufficiently soluble in water were dissolved in isotonic saline and administered in volumes not greater than 0.5 cc. per 20-gm. mouse. If aqueous solubility was limited, mechanical grinding and suspension in 5 per cent gum arabic (U.S.P. XII) in saline were employed. By this method homogeneous suspensions were formed for a time sufficient to allow the accurate filling of hypodermic syringes. Rarely, when insoluble compounds suspended poorly in gum-arabic solutions, other procedures were used to achieve homogeneity of the administered material. Pairs of mice were given single injections of 512, 64, 8, and 1 mg. per Kg. and observed for seventy-two hours. The results of this acute primary ranging procedure allowed the choice of a dose level suitable to use in tests of toxicity on repeated administration.

On the basis of the preliminary study, five or six adjacent dosages were selected from the following series: 512, 256, 128, 64, 32, 16, 8, 4, 2, and 1 mg. per Kg. If necessary the series was extended below the last value. Animals were injected once daily for seven successive days in groups of three animals at each dose level. They were weighed before the test, at its conclusion, and once more seven days later. Loss of weight was considered indicative of toxicity but was not taken into account in arriving at the maximum tolerated dose which was the largest amount that could be administered on seven successive days without fatality.

The schedule of administration used in the toxicity test (seven daily doses) did not correspond exactly to the schedule used to establish the chemotherapeutic value of the compound against mouse leukemia, which involved injections three times weekly to a total of ten. The schedule employed in the toxicity determinations was chosen as a compromise between the procedures recommended for two different screening methods.

In testing compounds for their value against leukemia, groups of ten mice each were employed. Treatments were begun forty-eight hours after the inoculation of leukemic cells. One group was used as an untreated control and the animals in it were injected with normal saline solution, 0.2 cc. per 20-gm. mouse. One group was used as a standard treated control. The animals received, in 0.2 cc. saline, the maximum tolerated dose of a compound, the therapeutic value of which had been established by previous experiments. The remaining ten groups of mice each received the maximum tolerated dose of one of the ten compounds to be tested. Injections were given intraperitoneally three times weekly for ten doses. The mice were weighed weekly and the doses were varied according to weight on the basis of 0.2 cc. for a 20-gm. mouse. The animals were observed twice daily except Sundays. Those that died were autopsied and the spleen, liver, and lymph nodes examined for enlargement. If gross evidence of leukemia was clear-cut at autopsy no sections were made; but when there was doubt about the diagnosis, the liver and spleen were studied histologically.

All survivors were sacrificed at 100 days, a period chosen arbitrarily. This selection was made partly because of lack of storage space for animals and partly because of the fact that at any time subsequent to 100 days

* These determinations were made by Dr. Frederick Philips and Mrs. Marie Borgotta in the Department of Pharmacology.

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after inoculation, deaths from the transmitted leukemia could easily become confused with the spontaneous leukemia that begins to occur in this stock at about the fifth month of life. Of the 300 mice that survived to the termination of the experiments and so were killed at 100 days, 96.3 per cent showed no gross evidence of leukemia. These 100-day "cures" were included in the averages but also classed separately in Table 1 to show their relative frequency and to distinguish between them and delayed leukemic deaths.

In determining the average survival time of a group of mice, the figure for those dying of leukemia was first determined. The controls almost invariably (99.77 per cent) died of leukemia. Eleven of 443 control mice died of intercurrent disease. The omission of animals that died in this way accounts for the occasional inclusion of control results based on groups of less than ten mice. Treated animals that died of causes other than leukemia, before the time when leukemia would be expected to develop, were also omitted from the computations. Death in these animals may have been due to intercurrent disease or to toxic effects of the drug. Deaths from the toxic effects were inevitable from time to time, since a dose near the lethal level was employed as the one necessary to obtain the maximum therapeutic results. The omission of these animals from the average was considered justifiable on the grounds that in mice dying early from causes other than leukemia, the drug had not had a chance to act against the disease per se. Under these circumstances the time of death gave no indication of the therapeutic effectiveness of a compound under test. Deaths from causes other than leukemia, that occurred after the average time of death from leukemia, were, however, included in computing the final average survival time. Justification for this is found in the fact that since death was not due to leukemia but to some other cause, the compound prolonged the survival time of these mice from the standpoint of the leukemia. If the mice had not died because of the toxic effects of the test compound or of intercurrent disease, they presumably would have lived even longer and would have increased even more the average survival time of animals with leukemia. Late deaths not due to leukemia were not a problem in the case of the control animals. These almost always (99.77 per cent) died of leukemia if they survived to the fifteen- to thirty-day period necessary for the development of the disease. The percentage increase in survival time (I_x) was calculated by the formula

$$I_x = \frac{ST_x - ST_c}{ST_c}$$

where ST_x and ST_c are the average survival time in days of the treated and of the control groups respectively.

The inconstant results of different experiments in which the same drug was employed at the same dose level (Table 1) made necessary the inclusion in every experiment of a control observation in which a compound of known therapeutic effectiveness was employed. In a single experiment all mice with leukemia tended to show approximately the same therapeutic response to a test compound although different results were found in different experiments using the same strain of leukemia. This may well have been due to variations from experiment to experiment in the number of leukemic cells contained in the inoculum. If the control group treated with the standard compound showed an increase in survival of less that 50 per cent, the leukemia was considered to be too resistant to chemotherapy to allow an accurate evaluation of unknown compounds and the experiment was repeated.

In comparing the therapeutic value of a number of compounds tested in several experiments the relative chemotherapeutic index (R.C.I.) of each drug was computed as:

$$\frac{\%\text{ increase in survival time of mice treated with the given compound } (I_x)}{\%\text{ increase in survival time of mice treated with a standard compound (SK 101 or SK 137) } (I_s)}$$

The R.C.I. established for a compound gave only a rough index of the therapeutic value. This is demonstrated by the spread of values for SK 137 as shown in Fig. 3.

Compounds consistently giving an R.C.I. of less than 0.5 were usually discarded as not

meriting additional study. Those with indices greater than this arbitrary figure were or will be given a further trial with each strain of leukemia in use. For use in patients, it is probable that only compounds with an R.C.I. of greater than unity in some tests will be employed (Fig. 3).

Preliminary Observations on Methods

In order to evaluate the accuracy of the method, groups of approximately ten mice with each line of leukemia were injected with saline only. Average survival times ranged from 15.3 to 15.9 days in six groups with 1394 leukemia and from 24.1 to 29.9 days in five groups with 9417 leukemia. The constancy of the results attested to their validity as standards for comparison with those found in tests of materials of unknown therapeutic value.

In order to establish the range of survival times in groups of animals treated with the same compound in the same experiment, five groups of mice with each line of leukemia were treated with the same amount of SK 137. The average survival times of the groups injected with 1394 varied from 40.0 to 56.6 days. The increase in survival over the control values ranged from 115 to 200 per cent. The average survival times of groups of mice with leukemia 9417 treated with SK 137 varied from 37.0 to 41.6 days and the increase in survival from 53 to 72 per cent. Although there was considerable variation in the percentage increase in survival, rough comparisons of the chemotherapeutic effects of compounds are clearly possible by this method.

To evaluate the effect of variations in the amounts of compounds administered, two substances, SK 101 and SK 137, were tested at levels of 0.25, 0.50, and 1.0 maximum tolerated dose. Using 1394 leukemia and proceeding from the lowest to the highest dose level, the average survival times increased from 25.7 to 44.2 days with SK 137 and from 29.1 to 45.0 days with SK 101. With 9417 leukemia the increase was from 23.9 to 33.4 days with SK 137 and from 23.6 to 39.6 days with SK 101. Thus, in these experiments, the decrease from the entire maximum tolerated dose to 0.25 thereof lowered the R.C.I. from 1.0 to approximately 0.4. These data support the view that the maximum tolerated dose of a substance of unknown activity should be employed in order to obtain the maximum chemotherapeutic effect.

In the studies reported in this paper a total of 2127 mice were used in thirty-seven separate experiments. These do not include, however, the occasional experiments in which resistance to the standard chemotherapeutic agent appeared in the subline of leukemia employed. The results of experiments of this type were discarded and the experiments repeated for reasons previously discussed.

Of the 443 control mice, 430 died of leukemia, 11 of intercurrent disease before the time leukemia could be expected to be detectable, and 1 of intercurrent disease after this time with no signs of leukemia. Only 1, or 0.23 per cent was living after 100 days. In sharp contrast to this are 256 mice from the same experiments treated with SK 101, of which 85, or 33.2 per cent survived 100 days. Of these 85 mice, 84 showed no gross evidence of leukemia when sacrificed at that time. Of the 385 mice treated with SK 137, 74, or 19.2 per cent, survived for 100 days. In a total of 299 mice that were treated with these and other presumably active compounds and survived 100 days, 288, or 96 per cent

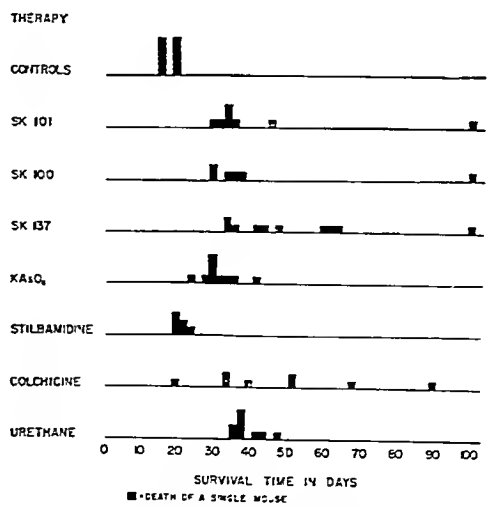


FIG. 1. *Scatter diagram showing time of death of mice in Experiment 1 (chloroleukemia Ak 1394).*

TABLE 1

EFFECT OF NITROGEN MUSTARD DERIVATIVES ON TRANSMITTED MOUSE LEUKEMIA

Expt.	*Drug*	*mg./Kg.*	*Total Mice*	*Deaths* Nonleukemic *Early*	*Late*	*Leukemic*	*100 day survival*	*Average survival time (days)*	I_x/I_s	*R.C.I.*
				LEUKEMIA 1394						
1	Control	—	10	—	—	10	—	17.5		
	SK 101	1.0	10	1	—	8	1	44.3	153	
	SK 100	0.5	8	2	—	5	1	44.5	154/153	1.005
	SK 137	4.0	10	—	—	9	1	51.8	196/153	1.28
	$KAsO_2$	7.5	10	—	—	10	—	31.1	78/153	.51
	Stilbamidine	75.0	10	4	—	6	—	20.7	18/153	.118
	Colchicine	0.625	9	1	—	8	—	48.3	177/153	1.16
	Urethane	1000.0	10	—	—	10	—	35.4	102/153	.67
2	Control	—	10	—	—	10	—	28.9		
	SK 101	1.0	10	1	—	1	8	95.5	230	
	SK 452	1.0	9	1	1	2	5	81.9	184/230	.80
	SK 437	0.5	9	—	—	1	8	95.0	228/230	.99
	SK 136	0.5	10	—	—	—	10	100.0	245/230	1.07
	SK 107	2.0	9	1	—	—	8	100.0	245/230	1.07
	SK 507	6.0	10	—	—	3	7	82.3	185/230	.80
	SK 497	2.0	10	—	—	2	8	86.4	199/230	.867
	SK 137	4.0	10	—	—	1	9	94.9	228/230	.99
	Testosteronc	62.5*	10	—	—	10	—	27.1	—6/230	—.02
3	Control	—	10	—	—	10	—	17.7		
	SK 101	1.0	10	—	—	10	—	39.8	125	
	SK 137	4.0	10	1	—	4	5	75.9	330/125	2.64
	SK 211	40.0	10	—	—	10	—	18.7	6/125	.048
	SK 437	0.2	10	—	—	9	1	49.3	177/125	1.42
	Teropterin	5.0†	10	—	—	10	—	20.1	8/125	.064
				LEUKEMIA 9417						
4	Control	—	7	—	—	7	—	27.6		
	SK 101	1.0	10	1	—	3	6	81.7	196	
	SK 137	4.0	10	—	—	8	2	56.8	106/196	0.54
	SK 100	0.5	10	2	—	7	1	52.3	90/196	0.46
	$KAsO_2$	7.5	10	1	1	3	5	76.9	178/196	0.91
	Stilbamidine	75.0	9	3	—	6	—	27.6	—6/196	—.031
	Colchicine	.625	9	2	—	2	5	86.9	215/196	1.1
	Urethane	1000.0	10	3	—	7	—	36.3	32/196	0.163
5	Control	—	9	—	—	9	—	20.5		
	SK 101	1.0	10	—	1	7	2	47.0	129	
	SK 137	4.0	9	—	—	8	1	37.1	81/129	0.63
	SK 437	0.5	9	—	1	8	—	32.0	56/129	0.434
	SK 136	0.5	7	—	—	7	—	28.1	37/129	0.29
	SK 497	2.0	10	1	—	8	1	36.9	80/129	0.62
	SK 507	6.0	10	2	—	7	1	34.1	66/129	0.51
	SK 452	1.0	8	—	—	8	—	26.9	31/129	0.24
	SK 107	2.0	8	2	—	6	—	31.7	55/129	0.426
	Testosterone	62.5‡	10	—	—	10	—	21.2	3/129	0.023
6	Control	—	10	—	—	10	—	22.2		
	SK 101	1.0	10	3	1	6	—	39.1	76	
	SK 137	4.0	10	—	—	10	—	39.2	76/76	1.0
	SK 211	40.0	10	—	—	10	—	26.0	17/76	0.224
	SK 437	.2	10	1	—	9	—	43.2	94/76	1.24
	Teropterin	5.0§	10	—	—	10	—	23.1	4/76	0.053

* injected subcutaneously q.d. × 23
† injected q.d. × 24
‡ injected subcutaneously q.d. × 22
§ injected q.d. × 24

were grossly negative for leukemia at autopsy. These data support the thesis that SK 101 and SK 137 have a definite chemotherapeutic effect against transmitted mouse leukemia.

Results

In presenting the experimental results the limitation of space made it impossible to tabulate all the data. Hence, the details of three fairly representative experiments with each line of leukemia are presented with the derived relative chemotherapeutic indices (R.C.I.) (Table 1). Scatter diagrams to show actual time of death of the test mice are given for two of these experiments (Figs. 1 and 2). In Fig. 3 are presented the R.C.I. for all compounds tested in order to facilitate the comparison of their chemotherapeutic activities.

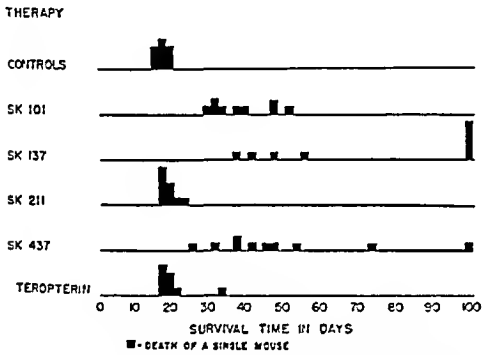


FIG. 2. *Scatter diagram showing time of death of mice in Experiment 3 (chloroleukemia Ak 1394).*

Comparative Therapeutic Values of Compounds of Different Groups. GROUP 1. Derivatives with the general formula

$$\begin{matrix} R \\ > N - CH_2CH_2Cl \\ R \end{matrix}$$

the mono (2-chloroethyl) amines, were relatively ineffective against both lines of transplanted mouse leukemia. Compounds SK 102, 301, and 415 were in this group.

GROUP 2. Most, although not all, of the bis (2-chloroethyl) amines with the general formula

$$R - N < \begin{matrix} CH_2CH_2Cl \\ CH_2CH_2Cl \end{matrix}$$

caused some prolongation of the survival time of the treated animals. SK 100, 101, 105, 108, 110, 112, 145, 146, 149, 498, 500, 502, 506, and 507 were among this group.

GROUP 3. SK 437, the only one of the bis (2-bromoethyl) amines of the type formula

$$R - N < \begin{matrix} CH_2CH_2Br \\ CH_2CH_2Br \end{matrix}$$

tested so far, was approximately as active as the chlorine analogue (SK 101).

GROUP 4. The tetrakis (2-chloroethyl) diamines thus far tested of the general formula

$$\begin{matrix} ClCH_2CH_2 \\ ClCH_2CH_2 \end{matrix} > N - R - N < \begin{matrix} CH_2CH_2Cl \\ CH_2CH_2Cl \end{matrix}$$

were also about as effective as SK 101, as evidenced by the data on SK 107, 136, and 137.

GROUP 5. SK 452, a tetrakis (2-bromoethyl) diamine of the general formula

$$\begin{matrix} BrCH_2CH_2 \\ BrCH_2CH_2 \end{matrix} > N - R - N < \begin{matrix} CH_2CH_2Br \\ CH_2CH_2Br \end{matrix}$$

demonstrated activity slightly less than that of SK 101.

GROUP 6. The same degree of activity was noted with SK 497, a tetrakis (2-chloropropyl) diamine of the type formula:

$$\begin{matrix} Cl \\ | \\ CH_3CHCH_2 \\ CH_3CHCH_2 \\ | \\ Cl \end{matrix} > N - R - N < \begin{matrix} Cl \\ | \\ CH_2CHCH_3 \\ CH_2CHCH_3 \\ | \\ Cl \end{matrix}$$

GROUP 7. SK 134, the only quaternary ammonium compound so far tested, had no therapeutic effect.

$$\begin{matrix} & Cl & \\ R & | & CH_2CH_2Cl \\ & > N < & \\ R & & CH_2CH_2Cl \end{matrix}$$

GROUP 8. Three compounds, colchicine, urethane, and potassium arsenite, previously shown to be therapeutically active against leukemia, were tested. Colchicine exerted an effect comparable to that of the more effec-

tive nitrogen mustards in tests with both lines of leukemia. Urethane and potassium arsenite were slightly less effective.

GROUP 9. Certain miscellaneous substances, stilbamidine, testosterone, 2-diethylaminomethylphenol (SK 211), teropterin, and both heat-killed and live cultures of *L. donovani* were without effect in these tests.

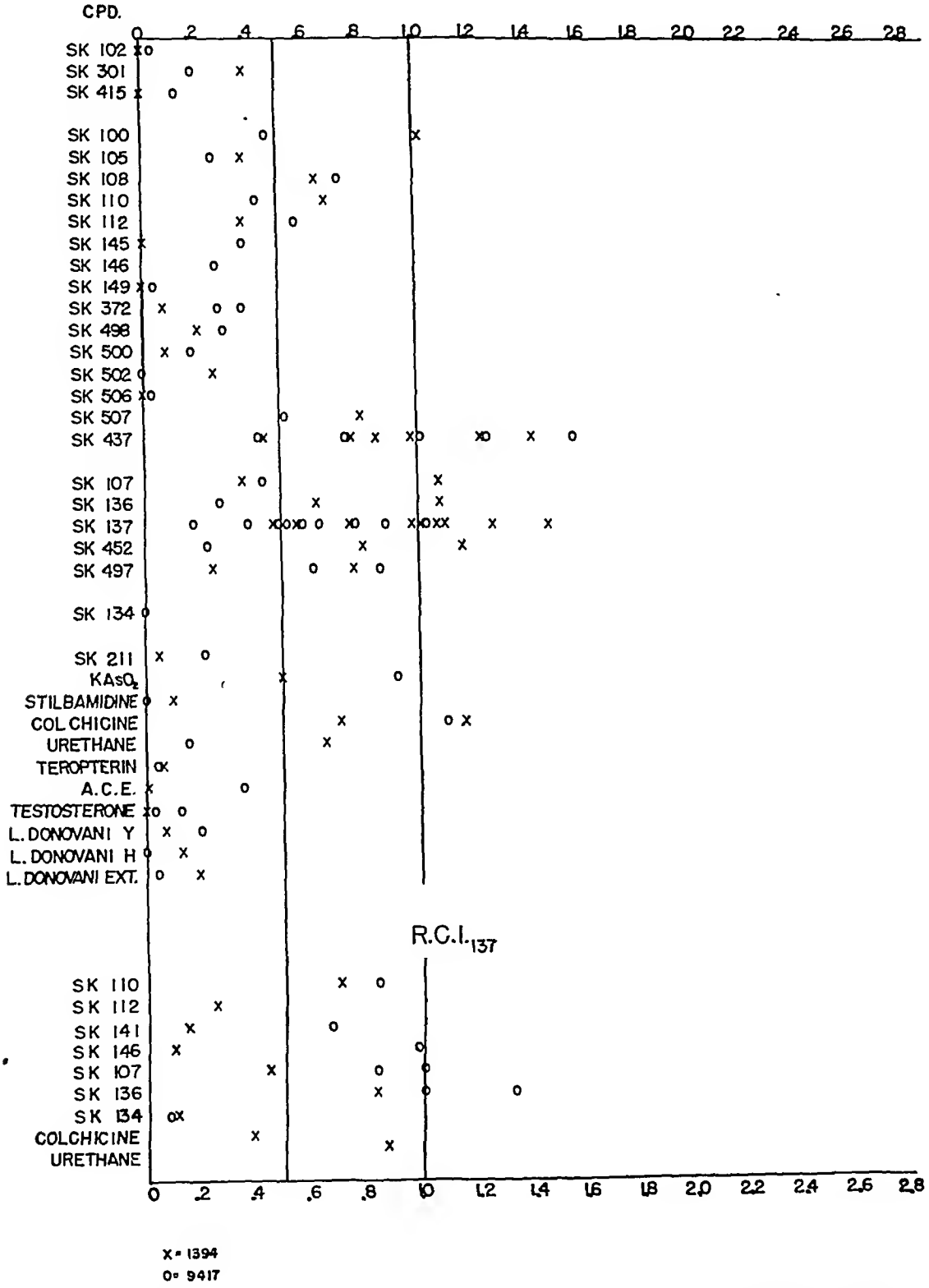
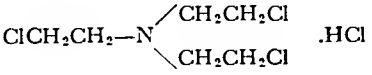
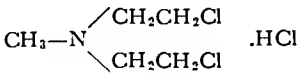
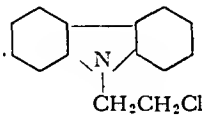
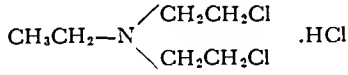
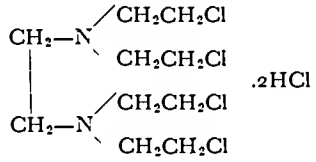
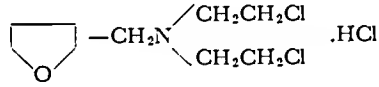
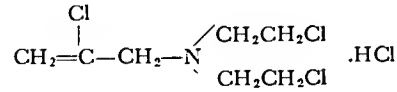
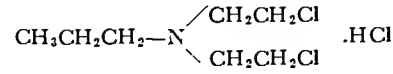
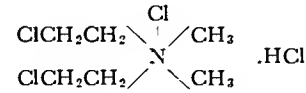
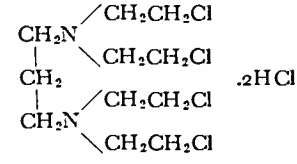


FIG. 3. *Diagram showing relative chemotherapeutic index of compounds using SK 101 or SK 137 as a standard of comparison.*

TABLE 2

THE CHEMOTHERAPEUTIC ACTION OF SUBSTANCES ON TRANSMITTED LEUKEMIA (AK 1394 AND AK 9417) IN MICE

SK No.	*Formula*	*Dose mg./Kg.**	*Range of values for R.C.I.*
SK 100		0.5	0.45—1.00
SK 101		1.0	arbitrarily set at 1.00
SK 102		200.00	0. —0.02
SK 105		0.5	0.25—0.37
SK 107		2.0	0.37—1.24
SK 108		0.5	0.64—0.73
SK 110		4.0	0.42—0.84
SK 112		0.5	0.25—0.56
SK 134		25.0	0. —0.12
SK 136		0.5	0.29—1.32

*Dose given intraperitoneally, three times weekly, for 10 doses.

TABLE 2—*Continued*

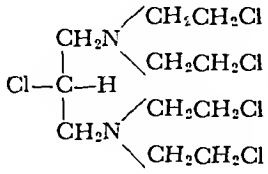
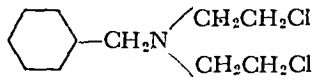
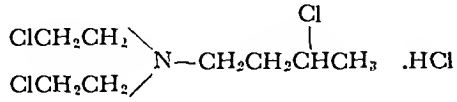
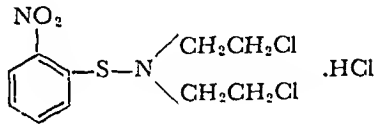
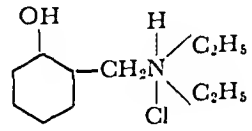
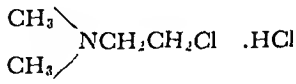
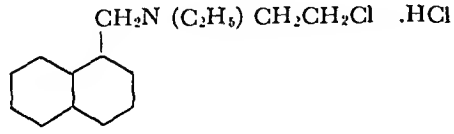
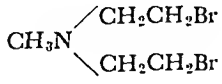
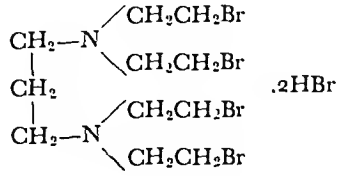
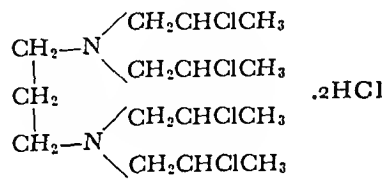
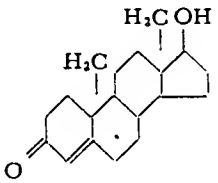
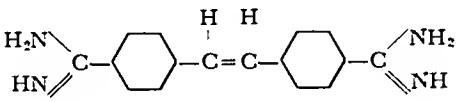
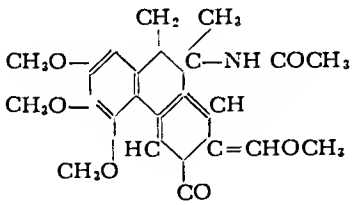
SK No.	*Formula*	*Dose mg./Kg.**	*Range of values for R.C.I.*
SK 137	 .2HCl	4.0	0.19—2.60
SK 145	 .HCl	5.0	0. —0.38
SK 146	 .HCl	2.0	0.10—0.98
SK 149	 .HCl	100.0	0. —0.
SK 211		40.0	0. —0.22
SK 301	 .HCl	150.0	0.18—0.36
SK 415	 .HCl	25.0	0. —0.13
SK 437	 .HBr	0.5	0.42—1.59
SK 452	 .2HBr	1.0	0.24—0.80
SK 497	 .2HCl	2.0	0.25—0.86

TABLE 2—*Continued*

SK No.	*Formula*	*Dose mg./Kg.**	*Range of values for R.C.I.*
SK 498	$CH_3(CH_2)_{11}—N(CH_2CH_2Cl)(CH_2CH_2Cl)$ .HCl	10.0	0.11—0.30
SK 500	$CH_3(CH_2)_5—N(CH_2CH_2Cl)(CH_2CH_2Cl)$ .HCl	3.0	0.09—0.17
SK 502	$CH_3(CH_2)_{15}—N(CH_2CH_2Cl)(CH_2CH_2Cl)$ .HCl	250.0	0. —0.25
SK 506	C_5H_{11}—C$_6$H$_4$—O—CH_2CH_2—O—CH_2CH_2—$N(CH_2CH_2Cl)(CH_2CH_2Cl)$ .HCl	2.0	0. —0.02
SK 507	C$_6$H$_5$—$CH_2CH_2CH_2N(CH_2CH_2Cl)(CH_2CH_2Cl)$ .HCl	6.0	0.51—0.80
Testosterone		62.5	0. —0.13
Stilbamidine		75.0	0. —0.12
Colchicine		0.625	0.4 —1.60
Potassium Arsenite	$KAsO_2$	7.5	0.5—0.90
Urethane	$NH_2—CO—O—CH_2CH_3$	1000.0	0.15—0.75
Teropterin		0.25 or 5.0	0. —0.05
Leishmania-donovani extract (heat killed)		50.0 cc.	0.04—0.19
Leishmania-donovani H, live cultures		50.0 cc.	0. —0.13
Leishmania-donovani Y, live cultures		50.0 cc.	0.19—0.21

Discussion

The procedure used in these studies has been under development for the past two years, and certain changes have been made as experience was gained.

Flory and Furth,[7] in their studies, used three types of myeloid and five types of lymphoid leukemia to evaluate chemotherapy, and in our procedure the screening of compounds against only two types of mouse leukemia is admittedly not ideal. However, taken in conjunction with the other screening methods run in parallel, we feel that it will provide sufficient breadth of base for a preliminary screening technique. It is granted that occasionally in these experiments a compound that has usually been active caused only a slight increase in survival time, in an isolated experiment against a single leukemia. This appears to be one of the weaknesses inherent in the method; but by using two different leukemias to test each compound we feel that the failures to detect active compounds because of such errors will be extremely rare. Since there are very few real leads at the moment, it is thought wiser to screen a large number of compounds superficially in an attempt to glean a few that are worth more careful study, rather than to examine exhaustively a small number of compounds in very few of which is there much reason to suspect real chemotherapeutic activity.

The cumulative effect of the nitrogen mustards is well known; hence, with these compounds, we were unable to give a much larger total dosage intraperitoneally by daily injections than by injections given three times weekly. Hence, since preliminary studies in this method were done largely with the nitrogen mustards, it was decided to use injection on the latter schedule. Further studies on compounds proving to be active on this schedule of dosage are under way at the present time to test the relative effectiveness of large doses given every ten days, or daily doses continued until the death of the animals. Not all these results are available as yet, so we are arbitrarily continuing to give injections three times weekly for ten doses. This means treating all animals until about the time when the controls are beginning to die. In some other classes of compounds where the cumulative effect is not so great, daily or even more frequent doses are given.

Underfeeding has been shown by Flory and Furth[7] in chloroleukemia Ak 1394 and in their lymphoid leukemias to cause an increase in survival time of no more than 50 per cent. Since mice treated with the nitrogen mustards in maximum tolerated doses frequently failed to gain weight as rapidly as did the controls and occasionally showed moderate weight loss, 50 per cent increase in survival time was set as the lower limit of a significant effect.

In many experiments SK 101 and SK 137 in maximum tolerated doses were run side by side. SK 101 was often somewhat more effective but at times SK 137 appeared to have more activity. This relative variation between the two derivatives was evident from the wide spread of values for the R.C.I. of SK 137 (Fig. 3). This demonstrated that the increase in survival time was only a rough means of evaluation and that moderate single variations between drugs were probably not significant. Single large or constant moderate variations did appear, however, to possess significance for the purposes of this study.

Since the immediate goal of this screening procedure is the development of clinical chemotherapeutic agents more effective than those available at present, the relative chemotherapeutic index (R.C.I.) was devised to facilitate the comparison of series of compounds with standard agents that were known to have a definite effect on leukemia in man. The standard nitrogen mustards, SK 101 and SK 137, both definitely prolong the survival time of mice with transmitted mouse leukemia. SK 101 which now has been used clinically throughout the country, in more than 1500 cases of neoplastic disease, is the preferable standard. SK 137, which has been tested many times and is nearly as effective as SK 101 against mouse leukemia (Fig. 3), has been used as the standard compound in a few experiments.

The screening of the nitrogen-mustard derivatives by this method has just begun and it is as yet too early to have definite ideas on

the mode of action of the various subgroups. The therapeutic activity of the compounds tested seems to be correlated with the ability to form the ethylene imonium ring and with the reactivity of this ring once it is formed.[12] Thus the quaternary ammonium compounds that cannot form the ring are inactive. The mono (2-chloroethyl) amine derivatives, although capable of ring formation, form one of low reactivity and their apparent lack of effectiveness may be explained on this basis The bis (2-chloroethyl) amines form a highly reactive ring and their chemotherapeutic activity also is apparent in these experiments. Increase in the relative size of the substituent group, however, whether alkyl or aryl, seems associated in most instances with decrease in activity. Studies of the dynamics of the tetrakis (2-chloroethyl), (2-bromoethyl), or (2-chloropropyl) amines or of the bis (2-bromoethyl) amines have not yet been completed, but from toxicity studies it is assumed that these compounds also act by a similar mechanism. Their therapeutic effectiveness was relatively high.

By this test method some of the bis and most of the tetrakis (2-chloroethyl) amines showed an activity roughly equal to that of colchicine and urethane. With SK 101, methyl-bis (2-chloroethyl) amine, chemotherapeutic activity against neoplastic disease has been well demonstrated both experimentally[5] and clinically,[13, 17, 20] but the beneficial effects have been limited by the toxic action on normal tissues. Many more of the nitrogen-mustard series are under study at the present time, and it is hoped that perhaps in some of these derivatives a dissociation between toxic and chemotherapeutic action may be found.

SK 101, urethane, and potassium arsenite all show activity by this screening procedure and all are useful chemotherapeutic agents in the treatment of clinical leukemia.[10, 20, 27] This, and the fact that SK 136, one of the several compounds that were found to be effective against mouse leukemia in these experiments, was also in some degree effective against leukemia in patients make it appear that it is possible to detect compounds of clinical value by this method.

Summary

1. A method for screening large numbers of compounds against transplated leukemia in mice, with a view to selecting those meriting clinical trial, has been described.

2. In evaluating unknown compounds, comparison in the same experiment was made with standard chemotherapeutic agents.

3. Nitrogen mustards with a single 2-chloroethyl group, and one quaternary ammonium compound gave negative results.

4. Teropterin, testosterone, stilbamidine, and leishmanial preparations were also negative.

5. Some nitrogen mustards containing two 2-chloroethyl, or two 2-bromoethyl, groups were chemotherapeutically active.

6. Five diamine derivatives of the tetrakis (2-chloroethyl), (2-bromoethyl), or (2-chloropropyl) compounds showed evidence of considerable activity.

7. Ethylcarbamate, colchicine, and potassium arsenite were also therapeutically active by this method.

8. No compounds definitely superior to methyl-bis (2-chloroethyl) amine (SK 101) were uncovered in this study.

9. The fact that ethylcarbamate, potassium arsenite, SK 101, and SK 136, all of which showed chemotherapeutic activity by this method, were also effective against clinical leukemia supports the hypothesis that this is a useful screening procedure.

nitely established. The development of spontaneous leukemia, and the mode of transmission and the development of the transmitted disease followed closely the descriptions of Furth [4, 18] no apparent deviations being noted.

The animals were autopsied when indications of leukemia were quite apparent. Preliminary criteria were size of spleen and lymph nodes as determined by palpation, clinical condition of the animal, and, occasionally, examination of blood smears. Final decision as to the status of each animal was reserved, however, until autopsy was performed. No animal was included in the leukemia groups unless there was definite hypertrophy of the spleen and lymph nodes. The thymic enlargement was found to be less constant, occasional animals showing all other signs of the disease but no marked thymic enlargement. In many cases, the leukemic status was further verified by passage of the disease to young mice of the same strain, as described by Furth.[4]

Control "preleukemic" mice were autopsied at ages approximately matching those of the leukemic animals. Most of these were young enough that there was no possibility that spontaneous leukemia had ensued. Nevertheless all were carefully examined at autopsy for signs of the disease and any doubtful cases were discarded.

At autopsy the adrenal glands, spleen, thymus, liver, kidneys, and several representative sets of lymph nodes (cervical, axillary and inguinal) were carefully dissected out and weighed. As already mentioned, the weights of the spleen, lymph nodes, and liver were good indexes of whether or not leukemia was present.

The adrenals were immediately covered with 2 ml. of acetone-alcohol (1:1), finely ground with the aid of a small amount of sand and a stirring rod, and extracted with the boiling solvent. The extract was transferred to a 10 ml. volumetric flash with a bulb pipette and the extraction with hot acetone-alcohol mixture was repeated three times. The extract was cooled to room temperature, made up to volume and filtered through alcohol-washed filter paper. An aliquot of the filtered solution was used for total cholesterol determinations by the Sperry-Schoenheimer method.[21] Since it was found necessary to use an 8 ml. aliquot to determine the cholesterol content of a single pair of mouse adrenals, duplicate determinations were not possible. However, this procedure was deemed preferable to pooling adrenals from a number of mice.

When mice were treated with 11-dehydrocorticosterone,* they received daily subcutaneous injections of the steroid beginning at the time the animals were inoculated with leukemic cells and continuing until the time of autopsy. The doses given were 150 and 245 γ per day, in 0.10 ml. sesame oil, in the two experiments reported.

Results and Discussion

The data obtained from leukemic mice are compared. in Table 1, to those obtained from "normal" preleukemic mice of the same strain. The average figures for male and female mice are calculated separately because the well-known sex difference in adrenal weight appears to be correlated with a difference in cholesterol concentration.

In both sexes, the leukemic state was associated with a definite and signficant increase in the weights of the lymph nodes, thymus, and spleen as has been previously reported by Furth.[3, 4] Likewise, the liver was consistently found to be greatly increased in size. The weight and size of the kidneys, however, were not consistently altered. Possible reasons for this will be indicated later. The weights of the adrenal glands were definitely greater (42 per cent increase) in leukemic males than in the preleukemic males. However, the adrenal glands of leukemic female mice were only 6.5 per cent heavier than were the adrenals of preleukemic females. A second smaller series of leukemic females of the same strain showed (see Table 2) a somewhat greater increase in adrenal size while a small group of leukemic females of the related AF strain (Table 3) showed but little enlargement in adrenals as compared to preleukemic controls. It may be added that little emphasis

* The 11-dehydrocorticosterone was furnished by Dr. R. T. Major of Merck and Company, Rahway, New Jersey.

TABLE 1

EFFECT OF LEUKEMIA ON ORGAN WEIGHTS AND ADRENAL CHOLESTEROL

Mice	*No.*	*Age*	*B.W.*	*Adr.*	*Kid.*	*Liv.*	*Spl.*	*Lymph nodes* *Ax.*	*Ing.*	*Cer.*	*Thym.*	*Adr. Chol.*
		days	*gm.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*%*
AK ♂ preleukemic	20	109–314	27.3 ± 0.6	1.30 ± 0.06	192 ± 7	577 ± 17	21 ± 1	4 ± 0.3	4 ± 0.3	5 ± 0.4	9 ± 2	2.96 ± 0.34
AK ♂ leukemic untreated	18	99–309	23.7 ± 0.4	1.85 ± 0.11	191 ± 6	964 ± 45	171 ± 15	19 ± 2.6	19 ± 3.2	38 ± 5.7	79 ± 39	1.38 ± 0.17
AK ♀ preleukemic	22	115–350	23.9 ± 0.7	2.14 ± 0.06	144 ± 3	590 ± 15	32 ± 5	5 ± 0.5	5 ± 0.4	7 ± 0.5	17 ± 3	5.70 ± 0.42
AK ♀ leukemic untreated (series 1)	24	131–363	24.2 ± 0.8	2.28 ± 0.07	166 ± 9	866 ± 68	172 ± 19	42 ± 8.6	40 ± 8.0	95 ± 19.0	162 ± 32	3.10 ± 0.32

Organ weights are expressed as mg. of fresh tissue per 10 gm. body weight.
The values given are for the mean $\pm \sigma_M$ where $\sigma_M = \sqrt{\Sigma d^2/n(n-1)}$.

TABLE 2

EFFECT OF 11-DEHYDROCORTICOSTERONE ON LEUKEMIC CHANGES

Mice	*No.*	*Age*	*B.W.*	*Adr.*	*Kid.*	*Liv.*	*Spl.*	*Lymph nodes* *Ax.*	*Ing.*	*Cer.*	*Thym.*	*Adr. Chol.*
		days	*gm.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*%*
AK ♀ preleukemic	22	115–350	23.9 ± 0.7	2.14 ± 0.06	144 ± 3	590 ± 15	32 ± 5	5 ± 0.5	5 ± 0.4	7 ± 0.5	17 ± 3	5.70 ± 0.42
AK ♀ leukemic untreated (series 2)	7	130–236	20.8 ± 0.5	2.78 ± 0.10	188 ± 4	1181 ± 36	230 ± 10	33 ± 1.9	30 ± 2.4	57 ± 2.0	28 ± 3	0.80 ± 0.09
AK ♀ leukemic 11-dehydro treated 245 γ per day	8	120–236	20.0 ± 0.6	2.46 ± 0.11	176 ± 9	1119 ± 53	211 ± 12	23 ± 1.6	20 ± 1.2	41 ± 3.1	17 ± 3	1.53 ± 0.37

Organ weights are expressed as mg. of fresh tissue per 10 gm. body weight.
The values given are for the mean $\pm \sigma_M$ where $\sigma_M = \sqrt{\Sigma d^2/n(n-1)}$.

TABLE 3

EFFECT OF 11-DEHYDROCORTICOSTERONE TREATMENT ON LEUKEMIC CHANGES

Mice	*No.*	*Age*	*B.W.*	*Adr.*	*Kid.*	*Liv.*	*Spl.*	*Lymph nodes* *Ax.*	*Ing.*	*Cer.*	*Thym.*	*Adr. Chol.*
		days	*gm.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*%*
AF ♀ preleukemic	13	200	25.2 ± 1.0	1.87 ± 0.11	162 ± 6	629 ± 14	50 ± 9	10 ± 0.4	8 ± 0.7	11 ± 1.6	19 ± 3	1.20 ± 0.12
AF ♀ leukemic untreated	8	200	25.5 ± 0.8	2.04 ± 0.10	162 ± 8	982 ± 140	223 ± 30	60 ± 10	46 ± 10	71 ± 14	158 ± 53	0.76 ± 0.08
AF ♀ leukemic 11-dehydro treated 150 γ per day	5	200	27.4 ± 0.4	2.14 ± 0.07	146 ± 6	1140 ± 84	249 ± 3	35 ± 4	28 ± 4	47 ± 5	88 ± 36	0.61 ± 0.06

Organ weights are expressed as mg. of fresh tissue per 10 gm. body weight.
The values given are for the mean $\pm \sigma_M$ where $\sigma_M = \sqrt{\Sigma d^2/n(n-1)}$.

is placed on this finding in the AF strain because these animals were of such an age* that many were developing spontaneous leukemia. The results obtained in the preleukemic AF mice may therefore have been modified by the imminent but as yet undetectable disease.

The reason for the differences between preleukemic male and female mice in adrenal cholesterol concentration is not apparent. It may well be, however, that the sex difference in adrenal size or the factor causing the sex difference in adrenal size may be linked in some fashion with the sex difference in adrenal cholesterol concentration. Incidentally it may be pointed out that with respect to kidney size a similar, but inverse, sex relationship apparently obtains. Thus, the kidneys of the preleukemic male AK mice were 25 per cent larger, when compared with due regard to body weight, than those of the preleukemic females. Both groups of leukemic AK females showed considerable kidney enlargement (15.3 and 30.6 per cent) compared to the preleukemic females. However, the onset of leukemia did not change the size of the male kidney. It should be emphasized that the sex difference in body weight does not account for sex differences in either adrenals or kidneys.

Comparison of the adrenal cholesterol concentration of the preleukemic and leukemic mice shows that regardless of the initial preleukemic cholesterol level, the adrenal cholesterol concentration of the leukemic animals in every group was 37 to 86 per cent lower than that of the preleukemic controls. The smallest change, a decrease of 37 per cent, was found in the leukemic AF females. Here again it should be noted that the preleukemic mice of this strain, although apparently healthy, were very near to development of discernable spontaneous leukemia. It is also interesting to note that the preleukemic controls of this group showed a very low cholesterol concentration. Because of this low level, perhaps related to the earliest but as yet undetectable stages of the disease, the absolute decrease found when the disease becomes apparent is minimized although these leukemic animals had the lowest adrenal cholesterol concentration of all the groups studied. It will be noted that the onset of the leukemic syndrome is associated with an increase in adrenal weight and a decrease in the cholesterol concentration of the gland. That the latter is not due solely to the increase in size is shown by calculating the total cholesterol content of the gland. Such calculations show that the total cholesterol content of the four groups of leukemic mice decreased by 34, 42, 82, and 31 per cent compared with their respective preleukemic control groups.

The results obtained by the treatment of mice with 11-dehydrocorticosterone were disappointing. As far as could be ascertained, administration of 150 or 245 γ per day, beginning immediately after transmission of the leukemic cells, had no effect on the course of the disease. The treated mice developed definite symptoms of the disease after the same interval as did the control mice that received leukemic cells but were not treated with the steroid. The organ weights (Tables 2 and 3) were apparently not influenced, the weight changes of the adrenals, liver, spleen, and kidneys being of approximately the same magnitudes as in the untreated leukemic mice. The increase in size of lymph nodes and thymus was possibly slightly inhibited, although the differences between the untreated and the steroid-treated animals are not significantly different.

The effect of the 11-dehydrocorticosterone treatment on the adrenal cholesterol concentration was not consistent. In the AK strain, the decrease in adrenal cholesterol accompanying the leukemic syndrome was apparently partially prevented by 11-dehydrocorticosterone. On the other hand, such treatment certainly did not prevent the loss of adrenal cholesterol in the AF leukemic mice. All in all, it is fair to conclude that the administration of 11-dehydrocorticosterone had little or no effect on the development of the leukemic syndrome, judged by any of the criteria used in the present study. It may also be stated that several animals, not included in this re-

* The AF mice, purchased from Carworth Farms, were ex-breeders approximately 6 months old. In this strain spontaneous leukemia develops at a somewhat earlier age than in the closely related AK strain.

port, were treated with purified adrenotrophic hormone* daily beginning at the time of inoculation with leukemic cells. Here again, no effect on the development of the disease was discernible. The only effect, noted at autopsy, was slight enlargement of the adrenals. Leukemic cells from these animals treated with adrenotrophic hormone, when transfused into untreated mice, produced leukemia in the same fashion as did leukemic cells from untreated mice. Why the present results differ from those of Murphy and Sturm[13] and of Heilman and Kendall[5] is open to conjecture. Admittedly, the compound administered differed from those used by these investigators. Although 11-dehydrocorticosterone has a good glycogenic effect in mice, it is possible that it is not so effective in preventing development of leukemic changes as, for example, 11-dehydro-17-hydroxycorticosterone, the compound reported by Heilman and Kendall to inhibit the growth of mouse lymphosarcoma. On the other hand, Murphy and Sturm reported that treatment with desoxycorticosterone, a steroid known to be practically devoid of glycogenic effect, exerted a positive inhibitory effect on transmitted rat leukemia. It is also possible that the differences are referable to the species of the host and the type of the transmitted disease rather than to differences in the substances employed. In any event, it is obvious that further experimentation is necessary if the discrepancy is to be clarified.

The relation of the adrenal cholesterol changes occurring coincidentally with the development of the leukemic syndrome which are reported here also need to be further clarified. It would be incorrect to conclude from the present results that the adrenal gland participates specifically in the leukemic syndrome. It is known[9, 17] that many conditions of stress result in at least temporary depletion of adrenal cholesterol, presumably as a consequence of increased conversion of adrenal cholesterol to the active adrenocortical hormones. It is therefore possible that the adrenal changes observed are merely the expression of a reaction to the stress of the disease process on the organism as a whole.

On the other hand, there are several indications that the changes in adrenal cholesterol in the leukemic syndrome are more specific. Although it is not apparent from the average figures given, inspection of the original data shows that the adrenal cholesterol concentration was not always proportional to the clinical condition of the diseased animal. Thus, animals appearing moribund frequently had higher adrenal cholesterol concentrations than others that were apparently in a fair state of health but on autopsy proved to be suffering from full-blown leukemia. In this connection it is again of interest to call attention to the group of preleukemic AF mice (Table 3). These animals were clinically perfectly healthy. At autopsy they showed no signs of leukemia. It was known, however, that many animals of this strain develop spontaneous leukemia at this age. In fact, several members of the AF "untreated leukemic" group were originally in the control group but at the time of autopsy were found to be definitely leukemic. Hence it appears likely that the development of the leukemic syndrome, even before it is recognizable, may be intimately related to the adrenal cholesterol level. It does not seem likely that the general stress in the organism would be very great at such an early date.

It is pertinent to mention here studies (to be published elsewhere) of the excretion of 17-ketosteroids by human leukemic patients. These steroids are recognized as being largely metabolic end products of the adrenocortical hormones. The results indicate that the excretion level of 17-ketosteroids is greatly decreased in lymphatic leukemia but not in other types. Furthermore, the decrease in 17-ketosteroid excretion was not correlated with severity of symptoms. For example, a patient practically moribund with myeloid leukemia still excreted normal quantities of 17-ketosteroids while very mild lymphatic leukemics, in a fair degree of health, excreted markedly diminished quantities of 17-ketosteroids.

It is conceded that other criteria of adrenocortical activity must be studied before a direct relation between the adrenal cortex and

* The purified adrenotrophic hormone was supplied by Dr. C. H. Li of the University of California, Berkeley.

the development of leukemia may be considered as established. The present results, however, do indicate the possibility of such a relationship.

SUMMARY

The development of lymphatic leukemia, whether spontaneous or transmitted, in mice of the AK strain is associated with a marked decrease in the concentration of adrenal cholesterol. The preleukemic adrenal cholesterol concentration is much higher in female mice than in males.

The developmental course of transmitted mouse leukemia is not altered by daily administration of 11-dehydrocorticosterone beginning at the time the leukemic cells are transmitted. The possible significance of these findings is briefly discussed.

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Primary Malignant Neoplasms of the Vesicovaginal Septum

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PRIMARY nonepithelial malignant neoplasms of the vagina are exceedingly rare. Although they may cause urinary symptoms, their occurrence is not mentioned in the standard urological texts and they are only briefly referred to in surgical and gynecological publications. For the most part, the literature on this subject is comprised of isolated case reports; only a few articles are at hand in which a wider study of the characteristics of these tumors has been undertaken.[1, 4, 11]

Of the nonepithelial vaginal tumors, sarcoma botryoides is the most commonly encountered type. It occurs almost always in children, but cases are on record where such tumors were observed in adults.[6, 8, 9] Whereas the histopathological picture of sarcoma botryoides is considered a well-established entity by most pathologists, it is evident from the study of the literature that other types of nonepithelial tumors arising in this region exhibit great variations in their microscopic appearance. McFarland, in his exhaustive study of this subject, tabulated 119 different terms that had been applied, by various authors, to the nonepithelial tumors of the urogenital region. He concluded that these tumors are dysontogenctic in origin and that they have "no standards of histological structure." He supports this theory by the fact that all these tumors contain undifferentiated embryonal cells in varying amounts, the true nature of which is obscure. Based on an analysis of his material, McFarland even concludes that sarcoma botryoides should be classified with the group of dysontogenetic tumors and not be considered a separate entity. A similar view is expressed by Almosch, as well as Murphy and DuShane, who advocate calling these lesions mixed mesodermal tumors, because they believe that the histogenesis is explained by the persistence of primitive mesenchyma or indifferent cells that retain pluripotential capacity for differentiation into various types of mesenchymal tissues.

While these neoplasms exhibit histological evidence of malignancy, they do not always grow aggressively, but slowly by direct extension into the adjacent structures. Distant metastases are fairly uncommon; however, their occurrence may be activated following incomplete surgical procedures.[11]

Primary nonepithelial tumors of the vagina may originate in any location, but reports in the literature indicate that they arise most often in the anterior wall. From this site of origin they may enlarge in the vesicovaginal septum from which they may involve the bladder and vaginal cavity.

Symptoms. It is obvious that the symptoms produced depend primarily upon the position of the growth. If the neoplasm develops in the inner portion of the vesicovaginal septum, it may attain considerable size before it causes symptoms, while it is more apt to be noticed at an earlier stage if it arises close to the urethra. Accordingly, neoplasms growing in the posterior portion of the vesicovaginal septum are usually not discovered early, except incidentally during the course of a routine pelvic examination. In the later stages, however, symptoms may develop as a result of involvement of the adjacent structures. If the tumor extends toward the base of the bladder, the patient complains of a sensation of pressure with or without frequency of urination. On the other hand, when the tumor infiltrates into the periureteral space, symptoms of progressive

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ureteral obstruction may ensue. In contrast, a tumor originating in the outer portion of the vagina may be more readily noticed by the patient during its asymptomatic stage. As the tumor enlarges, it encroaches upon the urethra, narrowing its lumen, producing increased urgency, hesitancy with progressive difficulty on urination, and eventually complete retention. Regardless of the position of these tumors, if they present themselves into the vaginal cavity, the mucous membrane may ulcerate, thus causing discharge with or without bleeding.

Diagnosis. Comparatively little difficulty is encountered in discovering the presence of a tumor in the vesicovaginal septum: Palpation and inspection of the anterior vaginal wall, supplemented by cystoscopic examination, will determine the location and the approximate extent of the tumor. Depending upon the position of the tumor, compression from without, possibly accompanied by elongation and distortion of the urethra, may be found, or, if tumor growth is confined to the inner portion of the septum, nothing but elevation of the bladder base may be noticed. Although infiltration of the bladder wall and urethra with resultant urinary retention is within the realm of possibility, such involvement need not occur even in quite extensive tumors. The degree of impingement upon the bladder wall by tumor growth may be demonstrated by cystograms or cystoaerograms taken in the anterior-posterior and oblique positions (Fig. 1 *A, B*). A complete study of the upper urinary tract must be performed in order to demonstrate possible ureteral obstruction that may have developed as a result of direct or indirect involvement of the ureters.

In order to establish the histopathological identity of the tumor, biopsy is essential. Tissue should be removed preferably through the vagina either by needle puncture or excision, but cystoscopic biopsy is also feasible when the bladder mucosa appears involved. If the interpretation of the first specimen leaves any doubt about the nature of the tumor, repeated biopsies from different areas should be made.

The differential diagnosis of neoplasms in the vesicovaginal septum depends upon whether or not the tumor is benign or malignant and whether it is primary or secondary in origin. Of the benign tumors, the fibroids are the most commonly encountered lesions; they occur most often during the third and fourth decades of life and are usually located in the anterior vaginal wall.[7] On the other hand, if the examination discloses

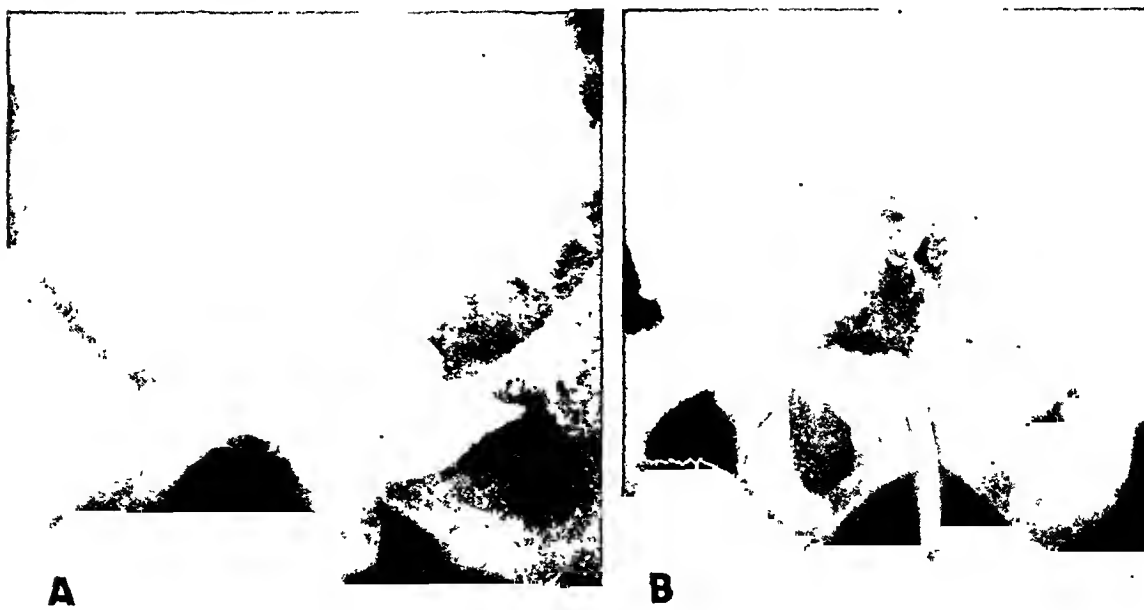

FIG. 1. A, *Cystoaerogram showing filling defect due to fibroid with calcification in the posterior part of the vesicovaginal septum.* B, *Cystogram in the right oblique position showing disfiguration of the posterior bladder wall.*

FIG. 2. *Distant initial manifestation of hypernephroma of the left kidney: metastasis to anterior vaginal wall.*

a malignant neoplasm, it should be kept in mind that the tumor may not be primary, but secondary in nature. In this event, the primary site may be found anywhere, for example in bladder, uterus, ovary, and, on occasion, in the kidney (Fig. 2). The following case serves as an illustration.

CASE REPORT

Mrs. M. B., No. 60648, was admitted to the Roswell Park Memorial Institute on July 14, 1947. Approximately three-and-a-half years prior to her admission, she developed gradually increasing hesitancy on urination with slowing down of the urinary stream. Examination at that time revealed that her symptoms were caused by a tumor in the anterior vaginal wall. Response to dilatation of the urethra was satisfactory at first, but one year later (May, 1945) persistent urinary complaints required surgical intervention. Following removal of tumor tissue through the vaginal wall, the patient remained asymptomatic, although dilatation of the urethra was necessary at monthly intervals to prevent recurrent obstructive symptoms.

Nevertheless, two-and-a-half months prior to her admission, she again experienced urinary difficulty that did not respond to dilatation of the urethra. On several occasions, she had complete retention that required catheterization. In addition, the patient noticed intermittent bloody serous discharge from the vagina. Her general condition remained unimpaired and there was no weight loss.

Examination revealed a thin individual, weighing 96 lbs. The physical findings were essentially negative, except for the pelvic lesion. The blood Wassermann was negative and blood count and blood chemistry yielded values within average limits of normal. The urine was clear, negative for sugar and albumen, and contained a few leukocytes; *Staphylococcus aureus* nonhemolyticus was obtained on culture.

Examination of the pelvic organs revealed the vulva and the external urethral orifice to be normal, but on palpation, a large tumor mass was felt through the anterior vaginal wall. The tumor was firm and resilient, resembling the rubbery consistency of prostatic adenoma. Its surface was smooth and depressed in the central portion. The growth was slightly movable, yet lateral extension was felt, spreading almost to the bony pelvis. Anteriorly, the tumor extended to a point 2.5 cm. proximal to the external urethral orifice and, posteriorly, a small sulcus separated it from the anterior lip of the cervix. The mucous membrane overlying the tumor was normal in appearance and examination of the uterus and adnexa was negative. Rectal examination confirmed the vaginal findings.

No involvement of the urethra was determined by palpation, but on passing a No. 24 French VanBuren sound, considerable difficulty was encountered in the posterior portion of the urethra, where the lumen was irregular and tortuous, owing to encroachment from without. On catheterization, no residual urine was obtained but marked elongation of the urethra was apparent.

Cystoscopic examination revealed elevation of the trigone and fundus of the bladder with both ureteral orifices demonstrable at the lateral borders of the elevated area. The mucosa of the bladder was intact throughout, but inspection of the vesical neck and posterior part of the urethra revealed some irregularity of the mucosa with edema and proliferative changes which were believed to be inflammatory in character. Several biopsies taken from that area confirmed this impression.

Study of the upper urinary tract disclosed good kidney function bilaterally and the normal outlines of the kidney pelves and ureters.

Biopsies taken from the tumor through the anterior vaginal wall revealed a malignant mesothelial growth composed of cell constituents identical to those of the neoplasm removed two-and-a-half years previously.

Based on the clinical and histological findings, a diagnosis of malignant mesodermal tumor of the vesicovaginal septum was made. In view of the known poor results obtained

in this type of tumor by external or interstitial irradiation, it was thought best to attempt surgical removal of the growth. To this end, an exploratory laparotomy was performed on August 19, 1947. During the course of the operation, it became apparent that the tumor was so intimately connected with the bladder and vagina that its complete removal was impossible without including these structures. It was then decided to alter the plan of operation to a much more radical procedure because it appeared possible, from the findings, to excise the tumor in toto if the bladder, internal genitalia, and part of the vagina were removed with the neoplasm. As a preliminary step, the left ureter was then implanted into the sigmoid before closure, and a second stage, right ureterosigmoidostomy was carried out three weeks later (September 9, 1947). Recovery from both operations was uneventful and excretory urograms disclosed well-functioning anastomoses on both sides with only slight dilatation of the kidney pelves and ureters.

Following thorough preparation of the patient, removal of the tumor, uterus, bladder, and anterior vaginal wall was carried out on October 28, 1947. (J.E.M.)

Surgical Procedure. Under ether anesthesia, a long transverse incision was made extending from one iliac crest to the other and the dissection was carried down to the peritoneum. The properitoneal space was developed distally down to the level of the fundus of the bladder in the mid-line and somewhat further forward laterally. The peritoneum was divided at this level, leaving a long anterior peritoneal flap. The small intestines were then packed off after they had been freed from the posterior surface of the uterus and broad ligaments. The ovarian arteries were secured laterally and the ovarian ligaments divided. The broad ligaments were sectioned down to the uterine arteries which were ligated and divided. The dissection was then carried laterally alongside the vaginal wall down both sides toward the vaginal outlet. The bladder was mobilized laterally and anteriorly, and the suspensory ligaments divided between ligatures. This allowed the bladder to fall away from the pubis. When the vesical arteries had been ligated, the mass, including the neoplasm, bladder, and internal genitalia, remained attached to the surrounding pelvic structures only by periurethral supports and vagina. With the laparotomy incision open, dissection was begun from below. The vagina was divided laterally on either side, beginning at the fourchette and extending bilaterally down behind the cervix, thus entering the pelvic peritoneal cavity. The urethra was encircled and the dissection carried up behind the arch of the pubis, dividing the remaining attachments of the bladder to the pelvis, thereby separating the remaining attachment of the specimen to the pelvis. When hemostasis had been obtained, a pack was introduced through the vaginal orifice and the operation on the perineum concluded. After a change of gown and gloves, the peritoneum was sutured down to the irregular base of the broad ligaments and the posterior lip of vaginal fascia, using continuous chromic sutures supported by occasional silk sutures. The abdominal wall was then closed, using interrupted silk sutures throughout.

Recovery from this extensive operation was slow but uneventful. The wound cavity closed *in gradually, showing fresh granulations, and* the patient was discharged from the hospital on December 22, 1947, in satisfactory condition. Her pelvic support consisted of granulation tissue arising from the long anterior peritoneal flap that had been used to close the peritoneal cavity.

When re-examined on February 2, 1948, she had gained 9 pounds. Urograms disclosed satisfactory anastomosis on both sides. No evidence of recurrent tumor was felt on palpation through the granulating vaginal tract.*

The surgical specimen removed consisted of uterus, bladder, anterior vaginal wall, and tumor. The tumor, which measured 4 × 6 × 8 cm., was well encapsulated (Fig. 3*A*). It had encircled the urethra completely without invading the urethral mucosa. It also was apparent from macroscopic examination that the tumor had not penetrated the mucosa of the bladder and vagina, and that extension of the neoplasm was confined to the vesicovaginal septum proper (Fig. 3*B*). The uterus was not involved.

Histological examination of the tumor (E. M. Burke) disclosed an infiltrating malignant neoplasm exhibiting marked variations in different locations. For the most part, the tumor cells were fairly large, possessed a granular cytoplasm, and were growing in flat plaques. In some areas the tumor cells were

* The patient was examined June 7, 1948. Her weight was 88 lbs. She had returned to work. She was voiding at three- to four-hour intervals during the day and once during the night. Examination revealed scarring of the posterior vaginal wall and clean granulation tissue in the anterior wall. There was no evidence of recurrent tumor.

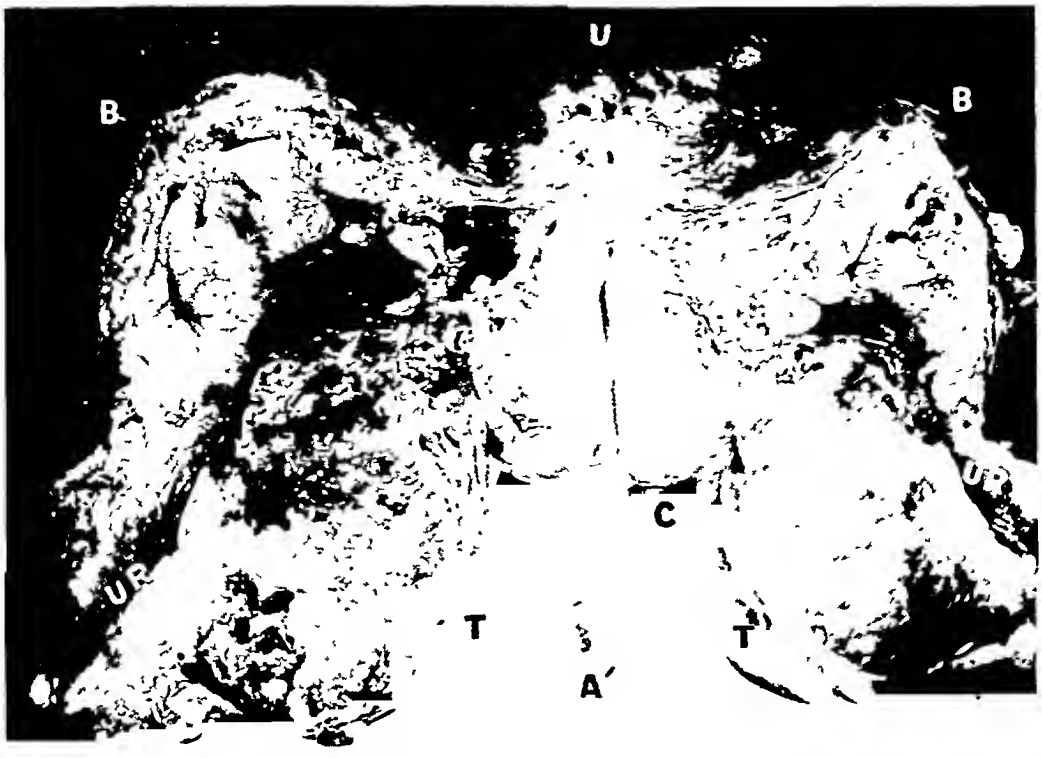

FIG. 3. A' *and* B', *Photographs of the specimen showing anatomical relationship between the tumor and the adjacent structures.* B. *bladder;* C, *cervix;* T. *tumor;* U. *uterus;* UR. *urethra.*

grouped around blood vessels and hemorrhages into the surrounding structures were seen. In other fields, where the tumor had infiltrated into the connective tissue, the cells appeared smaller and darker, some of them assuming spindle shape. In still other parts of the tumor, the aforementioned cell constituents were found in combination with signet-ring cells. The tumor which invaded the walls of bladder and vagina did not involve their mucous membranes. Cervix and uterus showed no disease (Fig. 4*A, B, C, D*).

Diagnosis: Malignant mixed mesodermal tumor of the vesicovaginal septum.

In view of the unusual features presented by this tumor, it was considered of sufficient interest to obtain opinions from leading pathologists. The following diagnoses were received: carcinoma simplex, low grade—probably arising from urogenital-ridge rest: malignant epithelial tumor, possibly on an embryonal basis: renal-cell carcinoma: metastatic adenocarcinoma; carotid-body–like tumor: metastatic hypernephroid tumor or a tumor arising on an embryonic malformation basis

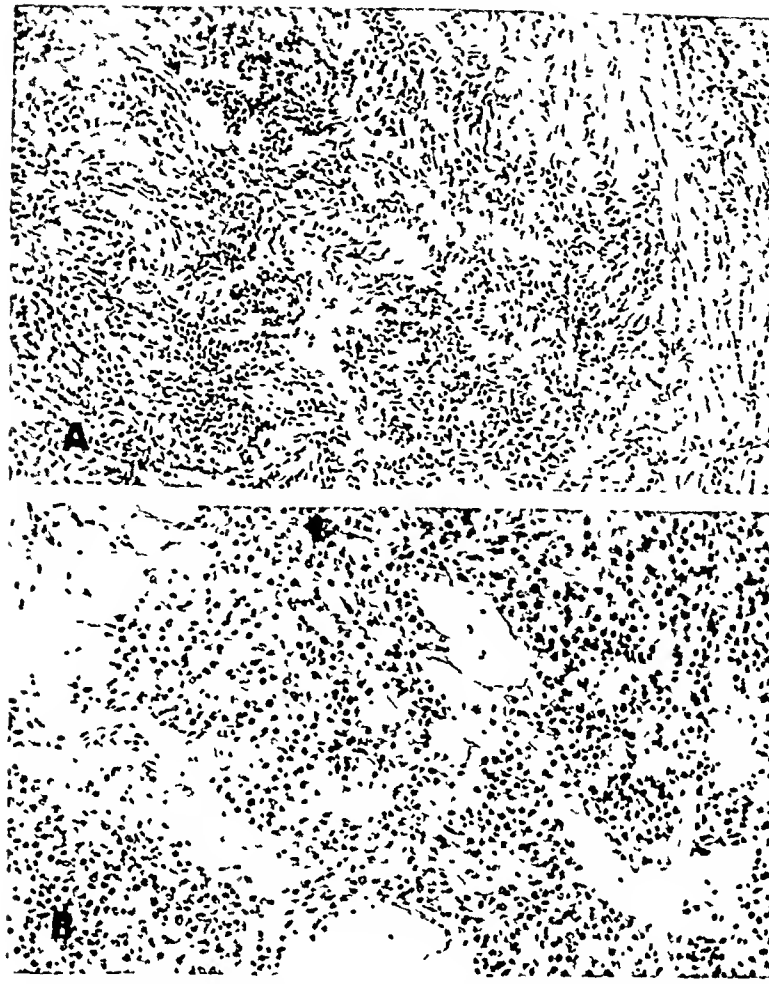

FIG. 4. *Photomicrographs of different portions of the tumor.* A, *Small malignant tumor cells invading fibrous connective tissue.* B, *Large, flat tumor cells separated by areas of hemorrhage.*

from genitourinary primordia in the rectovaginal and vesicovaginal septa.

DISCUSSION

In view of the short interval of time that has elapsed since operation, it is understood that no cure is claimed. Nevertheless, it is considered justifiable to report the case at this time because a primary malignant tumor in the vesicovaginal septum is very rare. In addition, this tumor exhibits unusual histopathological features.

The poor prognosis of mixed mesothelial tumors of the urogenital region has been emphasized by various authors, [1, 4, 5, 10, 11, 20] and only isolated reports of three- or five-year survivals are on record. [2, 3]

In general, the methods of treatment employed in the past have consisted of irradiation and surgery, either alone or in combination.

Since these neoplasms are partially comprised of radiosensitive cell elements of embryonal origin, an impressive degree of regression may be attained in some instances by the use of irradiation; however, resurgent tumor growth from the surviving radioresistant cell constituents is the rule. It must be appre-

FIG. 4. (Continued) *Photomicrographs of different portions of the tumor.* C, *Low-power view of vaginal wall and adjacent portion of the tumor.* D, *Low-power view of the bladder wall and adjacent portion of the tumor.*

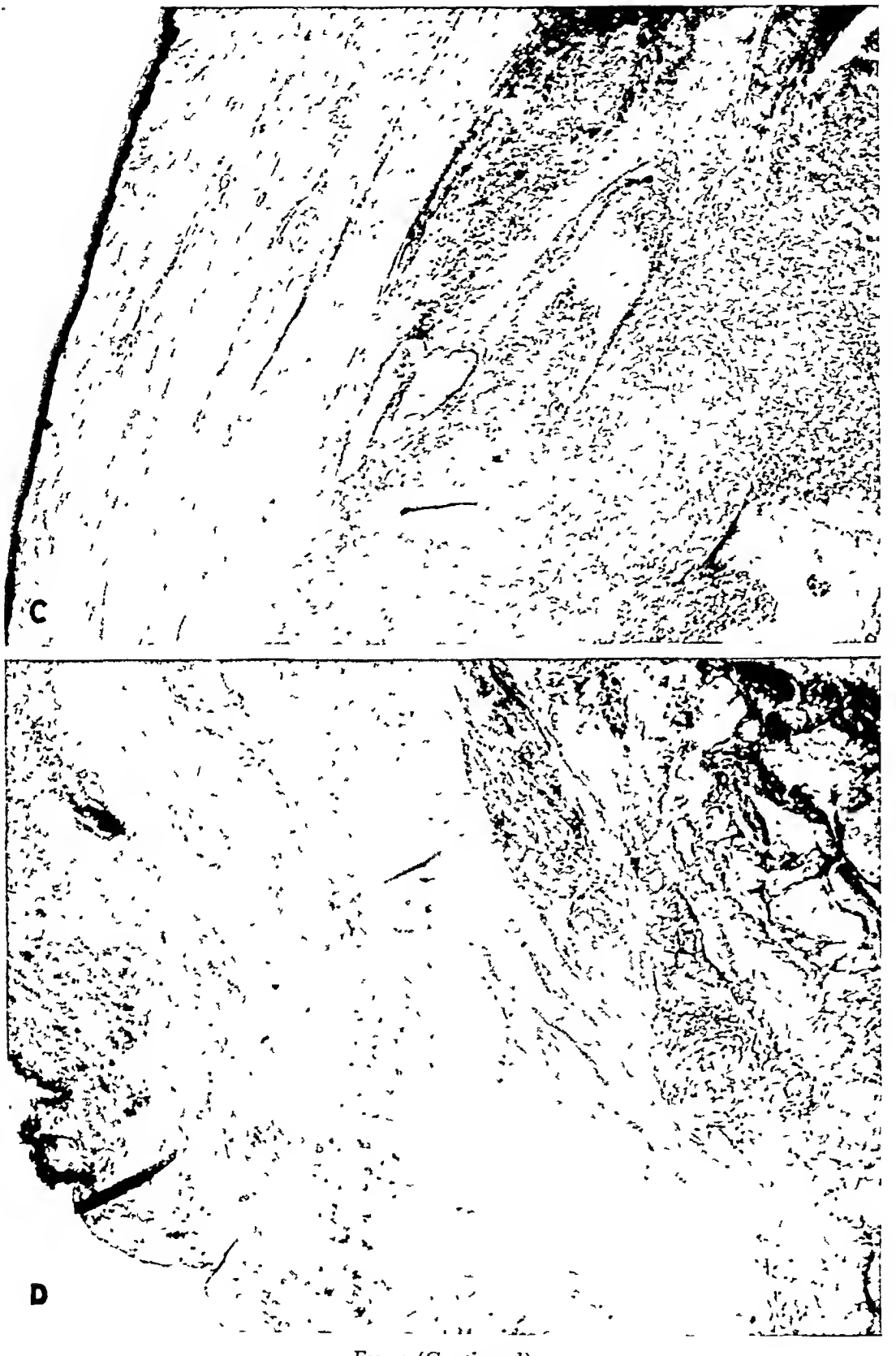

FIG 4 (Continued).

For caption see opposite page

ciated, therefore, that nothing but palliation should be expected from this form of therapy[1, 4, 10, 11, a.o.] and other procedures must be used to accomplish cure.

At present, it appears that surgery represents the most promising approach to eradication of the disease. Owing to the advances in modern surgery and anesthesia, it has become possible to undertake more radical surgery than heretofore. Although it remains to be seen whether or not the results obtained in this type of lesion can be materially improved by radical surgery, it may be assumed that the often discouraging operative results reported by various authors in previous years were largely due to limited and often incomplete surgical procedures.

In contemplating surgery, one must be well aware that these tumors may be much more extensive than can be determined preoperatively. While small and anteriorly located lesions may be extirpated from the vagina, it would appear more advantageous to avoid the vaginal route in favor of the abdominal approach in the larger and more posteriorly located. This permits the surgeon to determine the exact extent of the lesion and the degree of involvement of the adjacent structures. After a thorough exploration of the lesion encountered, the findings can be evaluated more accurately, and the surgical procedure can be decided accordingly.

It ensues from these considerations that one must be prepared for any eventualities before operation. In anticipation of possible extensive surgical procedures, it is imperative beforehand to secure the patient's consent. In treating these lesions surgically, one must keep in mind that incomplete surgery is more harmful than none and remember also that irradiation, although of great palliative value in inoperable cases, should not be employed preoperatively, because the resultant tissue reactions are apt to frustrate a subsequent attempt at radical surgical removal of the neoplasm.

Summary

Nonepithelial malignant tumors originating in the vesicovaginal septum are exceedingly rare. The great variations in the histopathological pattern of these neoplasms suggest that they are dysontogenetic in origin.

Symptomatology and differential diagnosis of these tumors are discussed with particular emphasis on the secondary genitourinary-tract involvement.

Surgical removal, to the extent of sacrificing the adjacent structures, if necessary, is advocated as the only method to accomplish cure.

One case of primary mixed mesodermal tumor in the vesicovaginal septum is reported.

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PANCREATO-TOTAL GASTRECTOMY AND SPLENECTOMY FOR ADVANCED CARCINOMA OF THE STOMACH

ALEXANDER BRUNSCHWIG, M.D.

THERE is general agreement that the results of surgery for cancer are improved when it is possible to resect widely not only the primary growth but also, and at the same time, those tissues to which direct spread is known to occur but has not yet taken place. The classic example of this is the situation in carcinoma of the breast. The radical operation of resection of the breast itself, the pectoral muscles, and the axillary contents en masse has yielded far better results than simple mastectomy, even when there is no gross evidence of spread beyond the breast.

In regard to the stomach, the nodes of the lesser and greater curvatures usually are the first to be involved by metastases. Following this, there is spread to the liver, greater omentum, and peritoneum of the upper abdomen. In advanced carcinoma of the stomach the author has been impressed by the rather frequent observation that the peritoneum over the body of the pancreas, and later the pancreas itself, becomes invaded by direct extension of the growth, and this extension may be observed at a time when there are no macroscopic metastases visible in the liver or over the general peritoneal surfaces. Such direct spread occurs through the fold of peritoneum that extends from the posterior aspect of the stomach to the anterior aspect of the body of the pancreas.

Because of the fact that at laparotomy, all of the tumor in such patients appeared to be confined to the stomach and body of the pancreas, an operation was planned to encompass the growth. This necessitated total gastrectomy, resection of the body of the pancreas, and splenectomy. The steps in such a procedure are as follows:

1. The high mid-line incision is extended below the umbilicus.
2. The pylorus is transected with invagination of distal end.

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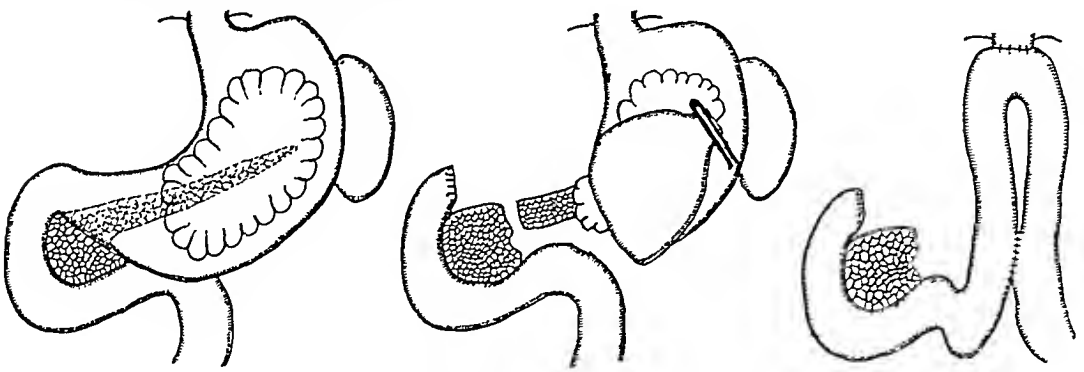

FIG. 1. *Schematic diagrams of pancreato-total gastrectomy and splenectomy. Left: Large carcinoma on posterior wall of the stomach that has extended backward onto the body and tail of the pancreas. Center: The pylorus has been divided, retracted, and the neck of the pancreas transected at the level of the superior mesenteric vein. In this manner the body and tail of the pancreas with the spleen are mobilized en masse with the stomach. Because of the extension of the gastric neoplasm into the pancreas, the latter remains adherent to the stomach. Right: Reconstitution of the upper alimentary tract following the operation. End-to-side esophagojejunostomy; entero-enterostomy between the efferent and afferent loops of jejunum. The head of the pancreas remains in situ.*

3. The spleen is grasped by the right hand and its diaphragmatic and colonic adhesions severed. It is thus elevated, bringing up the tip of the tail of the pancreas with mobilization of the upper portion of the greater curvature of the stomach.
4. Practically all of the greater omentum is freed from the transverse colon, so that all of the greater curvature of the stomach is mobilized.
5. The gastrohepatic omentum is divided as high as possible. The left gastric vessels are ligated away from the lesser curvature of the stomach.
6. The neck of the pancreas is transected at the level of the superior mesenteric vein. The splenic artery and vein are ligated at this level and divided.
7. The body and tail of the pancreas adherent to the gastric neoplasm are mobilized. During this step, the left adrenal gland is exposed.
8. The stomach, together with the adherent omentum, the body and tail of the pancreas and the spleen, is lifted upward over the xiphoid process. This exposes the posterior aspect of the abdominal esophagus.
9. The first long loop of jejunum is brought upward to the posterior aspect of the abdominal esophagus and sutured to it.

TABLE 1.

OPERATIVE RESULTS IN PANCREATO-TOTAL GASTRECTOMY WITH SPLENECTOMY

Case		*Survival after operation*
1. (D.)	Obtained satisfactory palliation; returned to normal occupation for 4 mos.	9 mos. Died of carcinomatosis.
2. (Fr.)	Obtained palliation; able to ingest food by mouth during entire survival period.	5 mos. Died of carcinomatosis.
3. (Chris)	Obtained palliation; gained 10 lbs. during survival period. (Transverse colon also had been resected.)	6 mos. Died of carcinomatosis.
4. (Un.)	Died of generalized peritonitis, 3d postoperative day.	Surgical mortality.
5. (F.S.)	Obtained palliation; able to enjoy ingestion of food by mouth during survival period.	3½ mos. Died of carcinomatosis.
6. (M.C.)	Two years previously had lower half of stomach resected for carcinoma. Second operation performed for relief of complete retention in gastric pouch. Transverse colon also resected. Obtained palliation.	6 mos. Died of carcinomatosis.
7. (B.C.)	Died of generalized peritonitis and bronchopneumonia, 5th postoperative day.	Surgical mortality.
8. (Z.)	Pancreato-total gastrectomy performed because mass in upper posterior portion of stomach adherent to the pancreas was thought to be carcinoma by x-ray and macroscopic inspection at operation. Specimen shows three conglomerated peptic ulcers and no evidence of carcinoma.	Living and well 2 yrs. 9 mos. after operation.
9. (I.B.)	Radical gastrectomy done 10 years previously for carcinoma. At recent operation remaining stomach, body of pancreas, spleen, transverse colon and loop of jejunum were resected. Obtained palliation.	6 mos. Died of carcinomatosis.
10. (Garl.)	Able to ingest food by mouth following convalescence from operation.	Lived 2 mos. Died of pneumonia. Recurrences present.
11. (Be.)	Obtained palliation.	Living 3 mos. No evidence of recurrences.
12. (Virg.)	Obtained palliation.	Living 4 mos.
13. (Miller)	Obtained palliation.	Living 5 mos.
14. (Hest.)	Brief palliation.	Living but has recurrences.
	Number of patients operated upon.... 14 Operative mortality ..... 2 Per cent surgical mortality 14.3%	

FIG 2 *Surgical specimen from case 11 (Be.) showing,* SS', *practically the entire stomach with a large carcinoma,* C, *that arose in the lower portion of the lesser curvature and extended backward to invade the mid-portion of the body of the pancreas.* PP', *the body and tail of the pancreas that were resected en masse with the stomach according to the technique illustrated in Fig 1 The level of transection at* P *is directly over the superior mesenteric vessels* TT' *segment of transverse colon, 10 cm. long, that was also involved by forward infiltration of the carcinoma through the transverse mesocolon.*

10 An esophagojejunostomy, using two rows of interrupted silk sutures, is performed and the specimen removed

11 An entero-enterostomy is done between the efferent and afferent loops of jejunum below the level of the transverse mesocolon

12 The abdomen is closed with a sump drain to the space in the left upper quadrant

Where extension occurs into the transverse mesocolon and onto the colon wall, the additional steps of resection of the transverse colon are carried out The two open segments (hepatic flexure and splenic flexure) are brought together as a double-barrel colostomy, which is closed later, or they are united by end-to-end anastomosis using two rows of interrupted silk sutures.

In all, the procedure has been carried out in fourteen patients, eight were operated upon while the author was on the staff of the University of Chicago Clinics: six patients are from his private service at the Memorial Hospital.

Results

The results of surgical treatment of cancer of the stomach still leave much to be desired when the lesions are relatively small, although there has been improvement over the years. When the lesions are large, there is still less optimism in regard to prolonged palliation. The results in the fourteen patients with pancreato-total gastrectomy are summarized in Table 1.

Discussion

The principal and outstanding complaint of all these patients was an almost complete inability to ingest solids or liquids by mouth. When this was attempted, nausea increased, epigastric pain became augmented, and vomiting followed by severe retching occurred. In Table 1, the statement that palliation was obtained indicates that ingestion of nutriment by mouth was again possible and was enjoyed without the distressing symptoms that obtained prior to operation.

The palliation that was obtained in most instances was for relatively brief periods. Thus, if gastric cancer is advanced and has involved the pancreas, the extended operation can hardly be expected to be more than a palliative procedure of limited promise. However, the experience reported here might serve to suggest a modification of the usual operation for earlier cancer of the stomach. In view of the tendency of these neoplasms to spread by direct extension to the body of the pancreas when there is still no macroscopic evidence of metastases to the liver or other distal foci, the question might be raised of the desirability of resection, en masse, of the body and tail of the pancreas together with the major portion of the stomach when carcinoma of the latter is present, especially in its lower and posterior portions. It would seem that this added step should not increase appreciably the surgical mortality and it would be in conformity with the generally accepted axiom of wide resection of malignant growths to include those uninvolved adjacent structures to which extension is known to occur readily. This step would constitute a corollary procedure to the wide resection of the greater omentum, a feature of radical gastrectomy for carcinoma that has now become routine with many surgeons.

Summary

A series of fourteen patients, in thirteen of whom carcinoma of the stomach was advanced necessitating total gastrectomy and resection of invaded body and tail of the pancreas, is presented to demonstrate that such a procedure is feasible. The suggestion is made that because of the relatively little added risk involved by removal of the body of the pancreas, this extra inclusion might be made in those instances of carcinoma of the stomach encountered on the posterior wall in which this direct spread has not yet occurred macroscopically and where there is no evidence of distal metastases.

THE ANATOMICAL DISTRIBUTION OF INTRAEPITHELIAL EPIDERMOID CARCINOMAS OF THE CERVIX

FRANK W. FOOTE, JR., M.D., and FRED W. STEWART, M.D.

THE concept of a noninfiltrating phase of carcinoma of the cervix appears to be gaining wider and, in the authors' opinion, well-merited acceptance.[1, 3, 5, 6, 8-12, 14, 16] Nor does it seem likely that this trend will abate in the predictable future; rather, it will probably parallel the growing nation-wide plea for diagnosis of cancer in its earliest stages. Moreover, the establishment of cancer-detection clinics in increasing numbers will add momentum, since, broadly speaking, cancer detection has more to offer in carcinoma of the cervix than in any other important form of human cancer.

Even after a carcinoma of the cervix has been detected in its noninfiltrative phase, there is the residual problem of how the very early cancer can be most logically and effectively treated. Certainly there is no general agreement among clinicians. Should one rely upon irradiation alone or should irradiation be combined with surgery? If surgical means are selected to the exclusion of irradiation, shall the procedure be trachelectomy, hysterectomy, hysterectomy with removal of adnexa, or should the more radical Wertheim operation be carried out?

All of these foregoing questions cannot be answered satisfactorily in this paper, but it is hoped that the study will furnish certain basic anatomical data that may be of some assistance when the problem of treatment presents itself.

PRESENT STUDY

During the past three years, twenty-seven pathological specimens of intraepithelial carcinoma of the cervix have been collected in the Memorial Hospital laboratory. For the most part, these specimens consisted of whole uteri, but the material includes the tissue from seven trachelectomies. Each has been studied pathologically according to a pre-arranged plan of sectioning that is briefly detailed as follows: On receipt of a specimen, the anterior and posterior lips of the cervix were identified and the entire cervix, sometimes with a portion of the uterine corpus, was fixed in 10 per cent formalin. Prior to fixation, photographs in color or in black and white were made when thought desirable. After fixation the cervix was cut in multiple sagittal sections that averaged about a millimeter in thickness and each tissue block was numbered. A typical cutting diagram of an average-sized cervix is shown in Fig. 1. If this method of total embedding of the cervix is

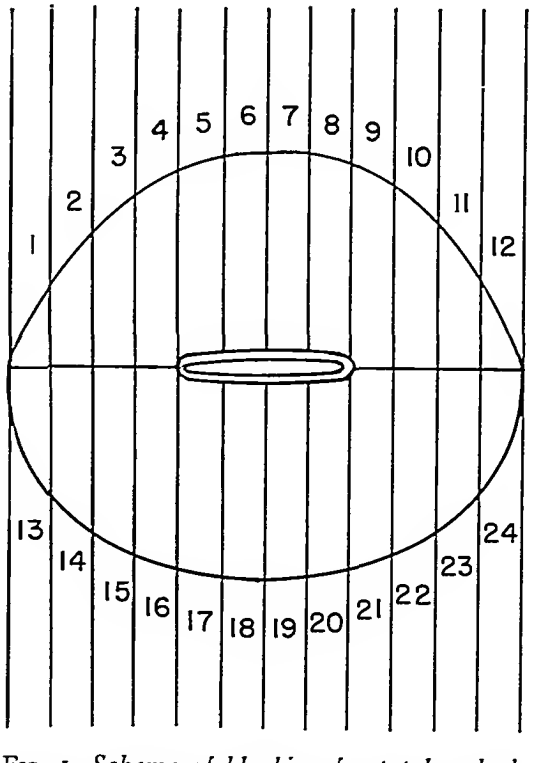

FIG. 1. *Scheme of blocking for total embedding of cervix.*

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carried out, the precise distribution of the noninfiltrating carcinoma can be studied microscopically in such a way that accurate reconstruction drawings are possible. Complete serial-sectioning was done only exceptionally, since this would have involved making literally hundreds of thousands of sections. The method employed is considered accurate for demonstrating tumor geography within the limits of about 1 mm. or less. It is readily seen that this mode of sectioning will make it easy for the pathologist to be certain whether or not complete excision of a lesion has been accomplished.

Before giving the anatomical findings it may be desirable to record certain clinical facts found in the case histories. The data immediately to follow concern twenty-four cases, each of which was treated at the Memorial Hospital. The anatomical findings discussed later will include twenty-seven cases, the material from three of which was put at our disposal by colleagues.

Clinical Data

The writers have been impressed, as have others,[7, 10, 11] with the fact that epidermoid carcinoma in situ is generally found at an earlier age than is symptomatic carcinoma of the cervix in its fully established, clinically diagnosable stage. The ages of the twenty-four patients in ascending order were: 21, 26, 26, 28, 33, 34, 35, 35, 36, 37, 37, 37, 38, 39, 39, 42, 42, 42, 42, 44, 47, 55, 64, and 69.

Eleven of the twenty-four patients whose clinical histories were available were entirely free of gynecological complaints. Of the thirteen patients who were not free of symptoms, eleven complained of some form of vaginal bleeding. This was mild in ten, rather severe in one in whom there was a coexisting uterine fibromyoma. One of the patients had vaginal bleeding supposedly dependent upon a recent abortion. In another, it was apparently functional in type. In the remainder with vaginal bleeding, erosion or chronic cervicitis offered the best explanation. The other two patients with symptoms complained only of vaginal discharge.

Visual examination of the cervix and palpation usually revealed nothing startling. In sixteen of twenty-four cases, the examiner described erosion of varying extent. This was by far the most frequent finding, and it was commonly combined with fissuring and multiple nabothian cysts. Leukoplakia was seen in three patients. Of particular note was the discovery that the clinical diagnosis in twenty of the twenty-four cases expressed no suspicion of cancer—the term "cancer" or "carcinoma" did not appear in the examiner's notes. In the other four a suspicion of the presence of carcinoma was recorded, but only twice was a provisional clinical diagnosis of carcinoma made. Many of these patients had been examined by several physicians.

Anatomical Findings

The distribution patterns of twenty-seven intraepithelial epidermoid carcinomas are shown in Figs. 2, 3, and 4. In fourteen cases the in situ carcinoma proved to be situated both on the portio vaginalis and within the endocervical canal. The outline of these fourteen in situ lesions is illustrated in Fig. 2.

In ten cases, approximately one-third of the series, the carcinoma in situ was limited solely to the portio vaginalis (Fig. 3).

Three of the twenty-seven cases had tumors limited to the endocervical canal, as shown in Fig. 4.

In this anatomical study it quickly became apparent that it was utterly impossible to detect with the naked eye exactly where the in situ carcinoma was situated or what its extent might be. This was true even though the pathologist knew at the time of his examination that the specimen contained a cancer. The four cases in the colored plate (Figs. 5-8) pointedly illustrate these statements. These cases are by no means exceptional, and essentially the entire series of cases would lend itself to similar illustration. The moral of the illustrations (Figs. 5-8) is obvious enough, namely, that one cannot visualize the location or distribution of in situ carcinomas of the cervix. As mentioned before, palpation likewise contributes nothing of value when one is dealing with this early form of carcinoma of the cervix.

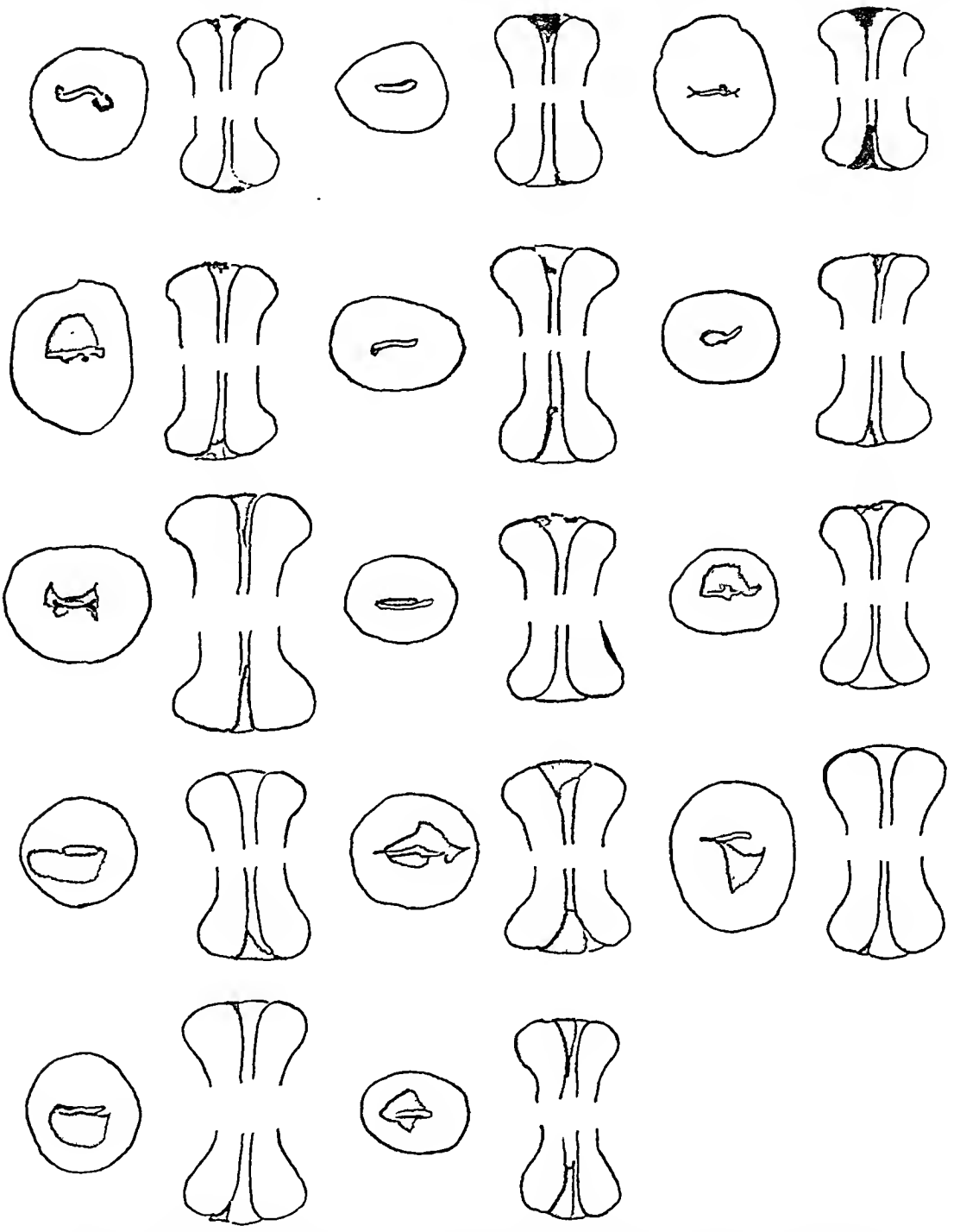

FIG. 2. *Distribution pattern of in situ carcinomas involving both portio vaginalis and endocervical canal.*

ANALYSIS OF ANATOMICAL FINDINGS

The anatomical findings diagramed in Figs. 2, 3, and 4 give concrete support to previously voiced impressions on the sites of localization of intraepithelial epidermoid carcinoma of the cervix.[3, 12, 15] They indicate clearly that these intraepithelial carcinomas are concentrated in a critical area that centers at and about the external os. Further review of the diagrams indicates that the por-

tio vaginalis is a more frequent site of origin than is the endocervical canal. Admittedly, fourteen of the twenty-seven cancers were situated on both the portio vaginalis and in the endocervical canal; in ten, however, the lesion was found exclusively on the portio, while only three were situated solely within the canal. It seems preferable to draw conclusions as to primary localization from the smaller groups, since these were generally more limited lesions and hence susceptible of more exact interpretation. One might surmise that the majority of those tumors involving both portio and canal actually began on the portio and extended into the canal.

In only one of these cases was it believed that the epidermoid carcinoma was present in two separate areas of the cervix. These tumors are diagramed in Fig. 2, upper left, and are believed to be independent primary tumors.

Sites for Biopsy

Owing to the difficulties in recognizing the location and distribution of in situ carcinomas by visual means the question is raised: At what sites should one blindly perform biopsy on an essentially innocent-looking cervix in order to insure the greatest "take" of positives in this occult phase of the disease? In Fig. 9 are four combinations that might be considered in answer to this question.

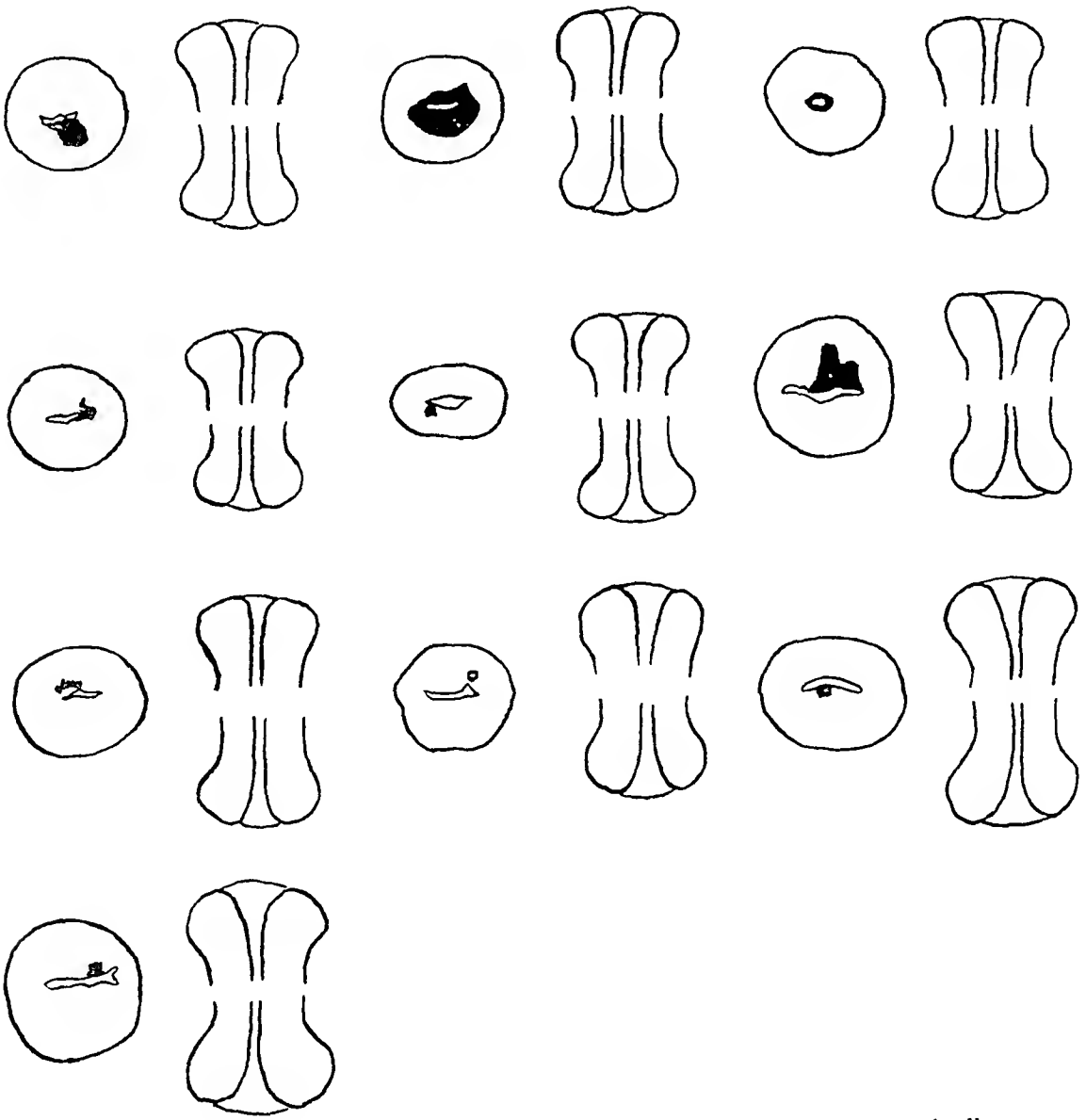

Fig. 3. *Distribution pattern of in situ carcinomas limited to portio vaginalis.*

Based on the anatomical studies reported here, if one selected for biopsy the central junctional area of the anterior or the posterior lip, either one of these two sites would have produced about thirteen positive pathological reports. If specimens were simultaneously taken from both these locations, twenty of the twenty-seven cases would theoretically have been reported as positive. If, in the biopsy desired." Hence, in three of eight cases studied by smear methods, the smear report was the first evidence of the presence of cancer recorded on the patients' charts. It is worth noting that in two of the three positive smear reports, the material was taken directly from the cervix and not from the vaginal vault. In the five cases reported as negative, vault material only was examined.

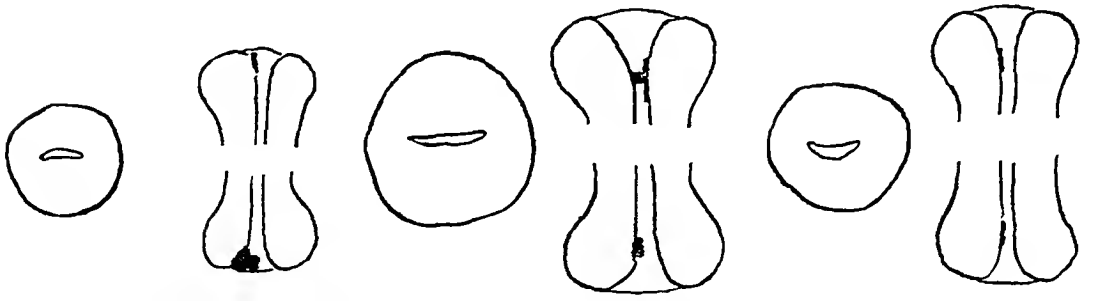

FIG. 4. *Distribution pattern of in situ carcinomas limited to endocervical canal.*

biopsy scheme, material was also taken from the lateral angles of the external os, twenty-five of the twenty-seven cases would presumably have been positively reported.

Three of the cases had lesions limited solely to the endocervical canal. In one, the tumor had extended to the external os and this seems to have accounted for the positive biopsy that was secured. In the second, the tissue received by the laboratory was labeled "endocervical biopsy." In the third case, two cervical biopsies were reported as negative. A positive diagnosis of carcinoma was reported after examination of an endocervical smear. This patient had a uterine fibromyoma and, for this reason alone, a hysterectomy was done in spite of the fact that there was no positive tissue diagnosis of carcinoma other than the smear.

SMEAR VS. BIOPSY IN THE DIAGNOSIS OF IN SITU CARCINOMA OF CERVIX

Smear methods of diagnosis were not routinely employed in this series of twenty-seven cases. In eight, however, smears had been taken before biopsies were made. In five they were reported negative. In two cases smears were reported as positive for cancer cells and in a third case the smears were reported as "suspicious, repeat smear and

Recent publications[2, 7] make it seem probable that in the eight cases that had smear examinations prior to biopsy, more positive reports would have been made had each had direct cervical smear examinations.

At the present time insufficient data are available to determine how important smear diagnosis may be in the detection of in situ carcinoma of the cervix. In reports already published[2, 4, 7] it seems that smear methods do offer some promise in the diagnosis of these early cancers of the cervix. Understandably, these very early lesions are more difficult of diagnosis in smears than are clinically established cervical carcinomas. There is at least fair evidence[2, 7] that direct smears of the cervix and endocervix are more reliable than the conventional vault smear. As matters now exist it seems fair to surmise that, in the nation at large, principal dependence for the detection of early carcinomas of the cervix must be placed on biopsy specimens. Future development of smear methods of diagnosis may temper this accent.

THE PROBLEM OF TREATMENT OF CARCINOMA IN SITU

Treatment is a difficult subject to discuss if for no other reason than that presented by the doubt lingering in some minds that the in

situ lesion is not necessarily an irreversible phenomenon, and that it may not inevitably lead to the infiltrating stage of carcinoma of the cervix. In a recent conference held in Boston under the sponsorship of the American Cancer Society, the subject of carcinoma in situ of the cervix provoked extended discussion. Members present at this conference had been invited from all sections of the country, and certainly the aggregate of opinions there represented could be described as authoritative. Certain querulous notes

FIGS. 5, 6, 7, 8. *Four illustrations that demonstrate how visual examination gives faulty impressions of the distribution or even the presence of in situ carcinoma of the cervix. The actual extent of the lesions is shown in red in the line drawings. Two of the cervices have been painted with Lugol's solution.*

were sounded by a limited number of those in attendance. It was proposed that clinicians be induced to follow up cases diagnosed as carcinoma in situ of the cervix, institute no treatment, and await developments. To us this seems of dubious propriety in spite of the growing body of evidence to the effect that a long latent period exists between the appearance of the in situ lesion and its eventual infiltration.[10-13, 16] If one reviews the literature, the critical analyst may well consider that sufficient follow-up observations now exist to prove the necessity for treatment rather than observation. A brief résumé of the work of Stevenson and Scipiades is in point. Stevenson and Scipiades reviewed some 10,000 sections of cervix from about 4000 cases. They found eighteen examples of noninvasive carcinoma of the cervix. Two patients developed invasive carcinoma after three and eight years respectively. These authors' further analysis of their material is of interest. They believed that in seven of the eighteen cases all of the carcinoma had been removed by various means. Of the remaining eleven, two (as already stated) developed invasive carcinoma. Five were recognized as carcinoma and had adequate radium treatment. Of the four remaining cases, two were given thorough cervical cauterization following biopsy and, in one of these, the lesion might well have been removed by the extensive "stripping" of the squamous epithelium from the portio and the curettage of the cervical canal. This leaves two cases unaccounted for, cases 5 and 11. Case 5 could not be followed, and case 11 was free of evidence of invasive carcinoma six years after diagnosis. The summary of case 11 does not disclose whether or not repeat biopsies were examined. A follow-up period of six years is impressive but does not close all issues.

Similar pertinent observations have been reported by Smith and Pemberton. They discussed sixteen cases of early cervical cancer which they stated corresponded to the types described by Cullen and Schiller,[9] namely, carcinoma in situ. Their case 1 had a trachelorrhaphy in February, 1916. This specimen was diagnosed pathologically as chronic cervicitis. In March, 1920, this patient had advanced carcinoma of the cervix. Review of the 1916 pathological material showed the previously overlooked cancer. In December, 1921, their case 2 had a trachelorrhaphy among other gynecological surgical procedures. Four years and nine months later she was treated for advanced carcinoma of the cervix. Review of the specimen of cervix removed in 1921, previously diagnosed as chronic cervicitis, showed early noninfiltrating carcinoma. Case 4 had an in situ carcinoma in 1929, initially overlooked by the pathologist, and was shown to have advanced carcinoma of the cervix three years and ten months later. In case 15, a pelvic operation including trachelorrhaphy was done in May, 1919. The cervix sections were diagnosed as chronic cervicitis but later study showed in situ carcinoma. Twelve years and six months later the patient had bloody vaginal discharge and a biopsy showed epidermoid carcinoma, grade II. In case 16, trachelorrhaphy was done in February, 1927. Sections showed in situ carcinoma. Six years and one month later complete hysterectomy was done in another hospital for carcinoma of the cervix. The patient died of this disease in September, 1933.

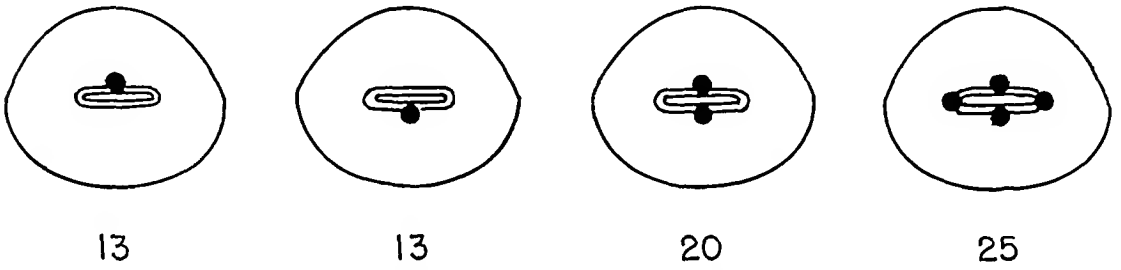

FIG. 9. *Preferential sites for biopsy of cervix. See text for explanation.*

Ten of Smith and Pemberton's cases were treated with radium. Hysterectomy was done in one. It is clearly evident from this summary that the cases that got into trouble were those that were not treated. Younge, in 1939, discussed the aforementioned work of Smith and Pemberton. He added two more examples of in situ carcinoma that progressed to the stage of infiltration after two and one-sixth and three and one-third years respectively. A recent paper of Taylor and Guyer may also be cited as adding observations of the same order.

If carcinoma in situ of the cervix is to be treated, what approach offers most to the patient? An important question immediately presents itself. How can one be certain that in any given case no infiltration is present? Obviously this question cannot be answered until complete pathological studies of the cervix have been made. If these pathological studies are not very precisely performed, the laboratory report may be inaccurate. How serious is the chance and hazard of finding infiltrating carcinoma in cases in which biopsies have shown only the noninfiltrating lesion? During the period in which the authors' twenty-seven cases were collected, the unexpected finding of infiltrating carcinoma of the cervix occurred on a single occasion. This patient had had a supracervical hysterectomy several years prior to 1948. In 1948, a biopsy taken in the Memorial Hospital examining clinic was reported as epidermoid carcinoma in situ. For this reason the remaining uterine segment was totally excised. Pathological examination showed a noninfiltrating epidermoid carcinoma occupying an extensive area about the external os. The in situ lesion also covered the entire cervical canal and in multiple sections small foci of infiltration, rather superficial to be sure, were found within the endocervical canal as far as 1.5 cm. above the external os. The infiltration referred to was extension of the tumor beyond the basement membrane. Had this case presented in a different setting, namely, in that of a woman who had not had a previous supracervical hysterectomy, and if the therapeutic procedure had been trachelectomy, the latter procedure would not have been sufficient to remove all foci of disease. This case is of course, not included in the group of twenty-seven cases under discussion.

It may be a matter of some surprise that more examples of infiltrating carcinoma were not discovered in our material. The literature includes one paper which might be considered as offering contradictory evidence, namely, that of TeLinde and Galvin. These authors discussed eleven cases of early carcinoma of the cervix. They reported the finding of invasion in ten of the eleven cases when the cervices were fully sectioned. They stated that in the eleventh case invasion was found in the biopsy. Careful study of the photomicrographs published by these authors showed many examples of tumor extending below the surface epithelium and continuing into the underlying cervical glands. The seeming discrepancy between their report and ours has been clarified in a personal communication with the senior author. TeLinde and Galvin applied the term "invasion" to extension below the surface epithelium and into the lower-lying cervical glands and did not use it in the sense of an extension beyond the basement membrane with actual infiltration of the fibromuscular stroma of the cervix. Study of our own material shows extension below surface epithelium in practically every case. Hence, if we used the term "invasion" in the limited sense employed by TeLinde and Galvin, we would have recorded a very high percentage of invasion. It is therefore clear that the apparent difference in findings is simply a matter of different usage of terms.

It is not within the province of the present authors, who are writing as pathologists, to make specific recommendations for treatment of carcinoma in situ of the cervix. Broadly speaking, ideas on treatment for this phase of the disease are in the formative stage. More abundant documentation will be required to settle many issues. However, some tentative generalizations appear justified: Many women with carcinomas in situ are in the age group justifying the expectation of five to ten years of active ovarian function. This cannot be preserved if irradiation treatment is utilized. It seems desirable that this

function be preserved. If this be true, what surgical means can be employed to control the disease without serious danger to the patient? In the pathological material here studied, hysterectomy with preservation of the adnexa would seemingly have been sufficient treatment in every case. More radical pelvic surgery can scarcely be justified if one can be assured that the lesion is truly noninfiltrating. Can any surgical means short of hysterectomy be expected to control this disease satisfactorily? To propose surgical treatment less extensive than hysterectomy can be justified on the grounds that the in situ carcinoma is in a preinvasive stage and hence the fear of metastasis can be excluded from the mind of the operator. The sole problem is the removal of the surface lesion and its extensions by continuity into gland ducts and lumina. Certainly trachelectomy would have been sufficient in most cases, if our anatomical studies can be used as a guide. This procedure was employed in seven cases. Any surgical means short of trachelectomy cannot be supported. Cauterization or simple coning is distinctly risky due to the utter inability of any observer to delineate either the internal or external limits of the noninfiltrating lesion. Too much emphasis cannot be laid upon the necessity for adequate and thorough pathological study of the cervix or entire uterus, depending upon the type of specimen received, so that the clinician is furnished with a reliable report of the distribution of the lesion.

It seems that hysterectomy with preservation of adnexa is the one procedure most generally suitable. Trachelectomy can also be substantially supported on anatomical grounds. The operator must, however, be prepared to do a more complete procedure later if pathological studies indicate inadequate removal of the tumor. Regardless of whether hysterectomy or trachelectomy is done, the surgeon should take the precaution to remove a cuff of tissue about the limits of the portio vaginalis. For example, in one of our own cases that was treated by simple hysterectomy at Memorial Hospital the in situ carcinoma extended in grossly undetectable fashion far out along the axes of two and three o'clock. The most external of the tissue blocks along this plane disclosed a small area of in situ carcinoma. It was necessary to cut this block serially before complete excision of the lesion could be demonstrated. Nearly 200 serial sections were prepared, each was labeled in order and the carcinoma only disappeared from view in section 92.

Summary

The anatomical distribution of twenty-seven in situ carcinomas of the cervix has been determined by topographic histological methods and the findings illustrated schematically. Sites for taking biopsies from cervices not showing grossly recognizable carcinomas are proposed. Smear methods in the diagnosis of carcinoma in situ of the cervix are discussed briefly. The implications of the anatomical findings in the choice of treatment methods of carcinoma in situ are presented.

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GLOMUS-JUGULARIS TUMORS

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CERTAIN primary tumors of the middle ear have been designated as endotheliomas and hemangioendotheliomas. These diagnoses have apparently been made by the process of exclusion, and some uncertainty has been felt regarding the accuracy of such terms.

This attitude is reflected by Marx, who stated that the type called "endothelioma" probably represents the most controversial type of tumor in the middle ear. The term, however, continues to be in general use even after Ewing's statement that "on analysis it appears that the various tumors which, at one time or another, have led authors to employ the term 'hemangioendothelioma,' fall readily into other groups, and that this term has a very limited application. . . ." In spite of this admonition, there have been more than fifty primary tumors of the middle ear placed in this category since Golgi's description in 1869.

It was not until 1941 that the problem was clarified by Guild, who announced a discovery that satisfactorily explains the identity of most of the tumors of this unusual group. He described a hitherto unknown structure in the temporal bone, which he named the glomus jugularis. This body is located in the adventitia of the dome of the jugular bulb immediately below the bony floor of the middle ear near the ramus tympanicus of the glossopharyngeal nerve. It usually measures 0.5 × 0.25 mm., and its innervation and blood supply are the same as that of the carotid body, namely, the glossopharyngeal nerve and the ascending pharyngeal artery through the inferior tympanic branch. Guild found that there is some variation in the size, position, and number of the bodies, but that histologically they vary individually only in degree of cellularity and vascularity. Because of the similarity between the glomus jugularis and the carotid body, he assumed their function to be the same, but no pertinent physiological investigation has been carried out yet.

A comparison of many serial sections of Guild's cases with sections of normal carotid bodies, carotid-body tumors, and all the hitherto reported cases of glomus-jugularis tumors, shows a striking similarity and only minute individual histological differences. In all of these, there is the same grouping of cells into an alveolar arrangement, surrounded by fibrous-tissue septa containing a variable number of large and small thin-walled vessels. The cells of the alveoli are large and polyhedral with small uniform nuclei that show no mitoses. This is seen by comparing the photomicrographs of the normal glomus jugularis in Figs. 1 and 2 with those of the tumors in Figs. 3 and 4.

Since a tumor of this type arises at the site of such a similar appearing body as the glomus jugularis, there can be little doubt about its origin. It appears logical therefore to refer to a growth of this type as a glomus-jugularis tumor in the same way that a growth of the carotid body is generally known as a carotid-body tumor.

That the tumors may arise from the glomus jugularis was first suggested by Rosenwasser in 1945. He described a benign tumor of the left ear in a 36-year-old man who had been deaf in that ear for ten years but had had no symptom other than purulent drainage from the ear for one month prior to examination. At the time of operation, the middle ear was found to be filled with a large purplish mass that appeared continuous with the wall of the posterior canal. The diagnosis was made by Otani, who recognized its resemblance to tumors of the carotid body and associated it with Guild's glomus jugularis.

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In 1947, LeCompte, Sommers, and Lathrop described the second benign tumor in a 43-year-old woman; and one month later Kipkie reported the third case in the left ear of a woman, 29 years of age, who had a concurrent carotid-body tumor on the right side. Both tumors from his patients were benign and histologically, as he points out, look basically the same.

Case Reports

The following appears to be the first case report of a malignant metastasizing glomus-jugularis tumor:

Case 1. This 54-year-old woman came under medical observation in July, 1935, at the age of 42 years. Her history is as follows:

In 1930, she had an attack of nausea, vomiting, and giddiness necessitating two weeks' bed rest and six weeks' convalescence. At that time, the drum of the left ear was red and bulging, and she had a burning sensation in that ear. In 1935, she developed a "breaking out" in the left auditory canal. This improved under local ointments. An attempt to clean up the ear and possibly obtain a biopsy resulted in profuse bleeding. For this reason, she was referred for roentgen-ray therapy. Roentgenograms of the skull and mastoids showed a marked difference in the appearance of the mastoids on the two sides. The cells of the left mastoid were quite cloudy and the septa more or less obscured. The left auditory canal had a cloudy appearance as compared with the right, and its bony walls were of a decreased density and had a somewhat roughened appearance. These findings were interpreted as being due to a "new growth" that involved the bony walls of the auditory canal. The clinical interpretation was cholesteatoma. For this reason, five, insignificant, "stimulating," 100 r doses of high-voltage roentgen-ray therapy were given to the ear at roughly monthly intervals.

In 1938, an area of "granulation" was noted on the anterior wall of the auditory canal. An attempt to fulgurate this area resulted in such profuse bleeding that two 6-mg. radium needles were packed against the "growth" for forty-eight hours. Following this, the "granulating area" healed.

In 1940, she was found to have a complete left facial paralysis. A roentgenogram of the left mastoid showed it to be partially sclerotic and the external auditory canal to be rough and irregular in outline.

In 1941, she was found to have loss of function of the left recurrent laryngeal nerve. At about this time, it was noted that she had complete loss of hearing in the left ear.

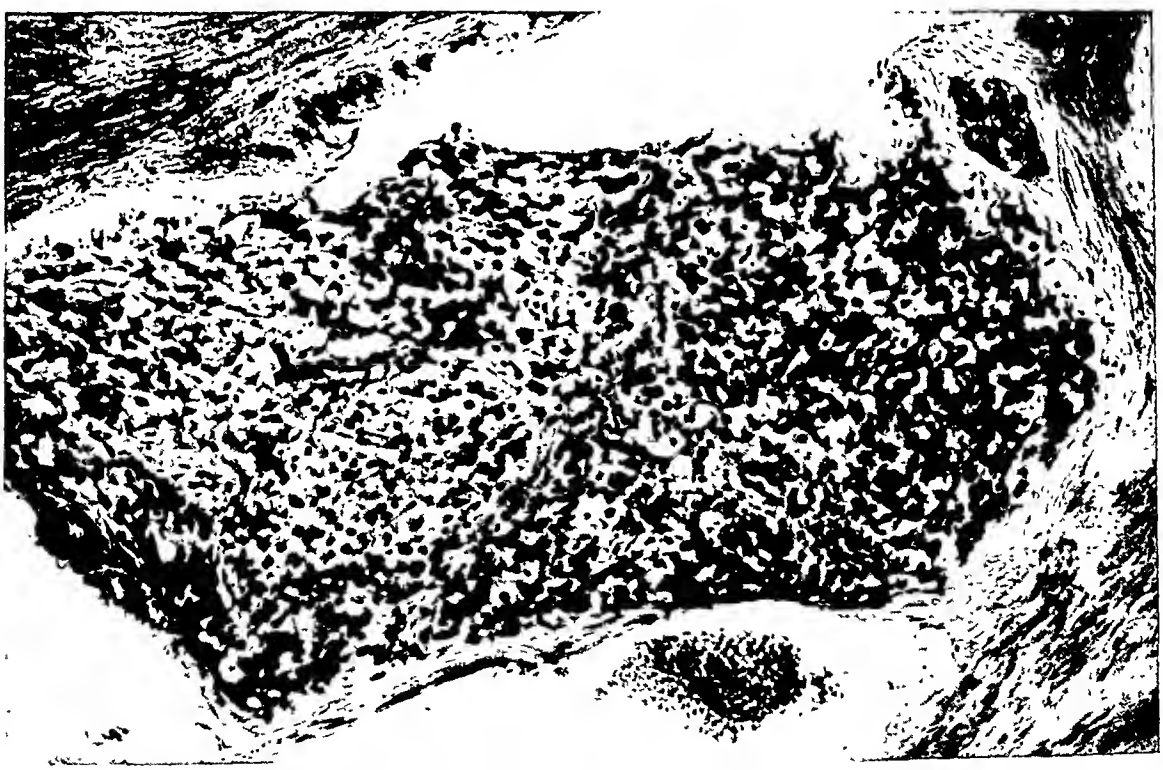

Fig. 1. *Photomicrograph of a normal glomus jugularis. (× 187.) (Courtesy of Dr. Stacy R. Guild, Johns Hopkins University School of Medicine.)*

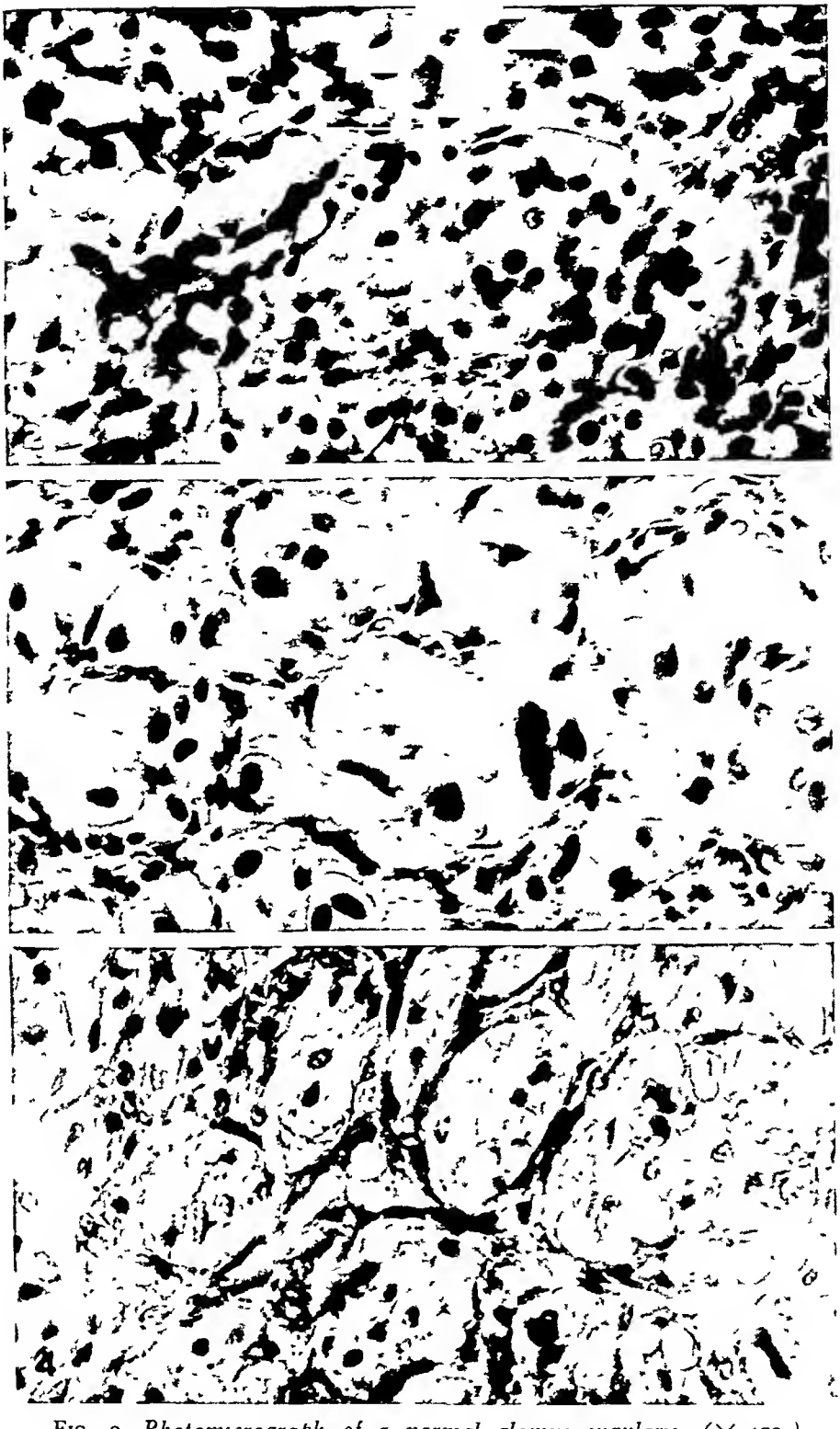

FIG. 2. *Photomicrograph of a normal glomus jugularis (× 450) (Courtesy of Dr. Stacy R. Guild, Johns Hopkins University School of Medicine.)*

FIG. 3. *Photomicrograph of a lymph-node metastasis from case 1 (× 450.)*

FIG. 4 *Photomicrograph of a benign glomus-jugularis tumor from case 2. (× 450.)*

In 1947, she developed several hard nodes in the upper left jugular chain, the largest measuring 3 cm. in diameter. At that time, the following abnormalities were noted: Neurologically there was a loss of function of the left seventh, eighth, tenth, eleventh, and twelfth cranial nerves and slight hypotonia of the left arm, with questionable adiadokokinesis. Roentgenograms of both mastoids and pyramids demonstrated extensive destruction of the left mastoid and the entire petrous pyramid. There was some new bone formation in the upper posterior cells of the mastoid where no bone destruction was seen. Most of the disease was centered around the external canal and posterior margins of the temporomandibular joint; the posterior half of the joint margin appeared destroyed. The chest seemed normal.

In August, 1947, the largest of the left upper jugular nodes was excised for microscopic examination. The only other significant physical finding was a grayish tumor mass just within and occluding the left external auditory canal. The patient refused to allow a biopsy of this area for fear of hemorrhage.

At present (seventeen years after the clinical onset) the patient has been given a trial of intensive, high-voltage, roentgen-ray therapy to the left mastoid area. The ataxia has increased during this treatment but the tumor has shown no regression.

Microscopically, tumor cells replace the entire lymph node, except for a narrow rim of subcapsular lymphoid tissue. The tumor is composed of nests of cells forming alveoli supported by a fine, fibrous network. van Gieson's stains show these alveoli to be composed of delicate strands of fibrous tissue, many of which are thickened by collagen, and a few solid masses of collagen that have been laid down near the large vessels and in the connective-tissue septa of the node. Many small blood vessels are in the alveolar walls, which are lined by normal-appearing endothelial cells. The cells comprising the alveoli vary in number from four to fourteen, are large and polyhedral, and have an indefinite cell boundary and a pale, eosinophilic cytoplasm with fine granules. The vesicular nuclei are round or ovoid; fine granules are seen, as well as one or sometimes two, large, round, prominent nucleoli. Few mitotic figures are seen; however, many of the nuclei are extremely large, pyknotic, and irregular, and scattered giant cells are present containing up to ten nuclei. The picture is that of a malignant tumor.

Wilder's reticulin stain shows fine reticulin fibers completely or partially surrounding some of the alveoli and completely absent in many others. Schmorl's stain proves the absence of chromaffin cells, and fat stains (Sudan IV) show no intracellular and almost no extracellular fat.

Case 2. This concerns a benign glomus-jugularis tumor followed for seventeen years.

This man, aged 81 years, consulted an ophthalmologist seventeen years ago at the age of 64 years because of a profuse flow of tears from the left eye. Since he had an obvious left facial paralysis, the patient was referred to Dr. W. H. Jenkins on January 8, 1931; he obtained a history of a four-year progressive loss of hearing, tinnitus, and dizziness.

The general physical examination was negative. Complement-fixation test for syphilis was negative. There was no hearing in the left ear for either voice or whisper, but hearing by bone conduction was very good. Aural examination revealed a small amount of thin, serosanguinous discharge in the left external auditory canal. Replacing the drum membrane and filling the canal was a red glistening mass about which an applicator could be passed and which appeared to arise in the middle ear. A roentgenogram showed clear mastoid cells and slight clouding in the area of the left mastoid antrum. A radical mastoidectomy was performed by Dr. Jenkins at Episcopal Hospital, Washington, D. C., on March 12, 1931. The entire middle-ear cavity was tightly packed with a dark-red, friable tumor which had no attachment except at the floor of the cavity, where it was attached to the jugular bulb at the site of a large opening in the bony floor. The mass was entirely removed only by excision of a portion of the jugular vein, bleeding being controlled by packing.

The postoperative course was uneventful. Two weeks after the operation an unknown amount of radium was placed in the middle-ear cavity. Within a few weeks there was complete healing.

At present, after seventeen years, there has been no recurrence, but hearing has not returned, nor has the patient regained the use of his facial muscles.

Microscopically, this tumor has the same basic pattern as that of case 1, but the alveoli are more regular and distinct. The cells of the alveoli are large, and the nuclei are

vesicular but do not show the disparity in size, shape, and staining qualities seen in the first case. This tumor appears definitely benign.

Comparative Microscopic Material

An effort has been made to obtain or review tissue or prepared slides from all the reported and known cases of glomus-jugularis tumors and also from cases reported as endotheliomas or hemangioendotheliomas that were suspected of belonging in this category. This includes material from the glomus-jugularis tumors reported by Rosenwasser, LeCompte et al., and Kipkie. Material from cases that are to be reported was sent to us by Poppen and Lattes. Capps kindly brought from London blocks of tissue from three cases that previously had been reported as hemangioendotheliomas, but which he agrees are glomus-jugularis tumors. Two of these are benign, and the patients are at present well and without recurrent disease. The third tumor is malignant. The patient, still living, has recurrent tumor, persistent facial paralysis, and bone destruction. She has been treated by surgical excision of the tumor followed by roentgen-ray radiation delivering approximately a 3000 r tumor dose. Proctor and Lindsay sent slides from one of their cases which had been called hemangioendothelioma. Microscopically, this is similar to the other malignant glomus-jugularis tumors and shows temporal-bone invasion.

Thus material on eleven cases of glomus-jugularis tumors has been collected and studied (Table 1). The cases are remarkably similar microscopically, with more or less distinct alveoli composed of varying numbers of large cells and many endothelial-lined blood vessels in the septa. As Guild pointed out for the normal glomus jugularis, these tumors also vary chiefly in their cellularity and vascularity. The cellularity is greater in malignant tumors as typified in case 1 and as is strikingly shown in the slides from Poppen's case.

Another variable is brought out with the use of van Gieson's stain. Although the glomus-jugularis tumor is not notably desmoplastic, there may be enough fibrous tissue and collagen present to cause some difficulty in diagnosis. This was most marked in Capps's case 1 and least conspicuous in our case 2. The diagnosis of malignancy in glomus-jugularis tumors is determined by the degree of invasiveness; the size, shape, and the pyknosis of the nuclei; and the presence of giant cells. Mitoses cannot be used as a criterion, since they are very rare even in the malignant tumors.

Primary tumors of the middle ear are extremely uncommon. Marx collected 155 cases, 15 of which were called endotheliomas. Furstenberg described 2 tumors of the middle ear found in 4,000 admissions at the University of Michigan, Department of Otology. Junod found 6 primary malignant tumors in 45,000 patients who came to the University Ear Clinic at Basel over a period of twenty-five years; and Robinson recorded 5 cases of tumor of the middle ear in 212,000 admissions at the Manhattan Eye, Ear and Throat Hospital in New York City. Approximately 55 per cent of these cases were designated as squamous carcinoma, 35 per cent as sarcoma of one type or another, and 10 per cent as endothelioma or hemangioendothelioma. While the diagnosis of squamous carcinoma is easily made and usually accepted, the diagnosis of sarcoma, endothelioma, or hemangioendothelioma in this particular location might be questioned. It is in these categories that cases are found that could be classified as glomus-jugularis tumors.

Table 1

CASES OF PROVED GLOMUS-JUGULARIS TUMORS

No.	*Case*	*Age*	*Sex*	*Malignancy*
1.	Rosenwasser	36	Male	Benign
2.	LeCompte, Sommers, & Lathrop	43	Female	Benign
3.	Kipkie	29	Female	Benign
4.	Capps	49	Female	Benign
5.	Capps	51	Female	Benign
6.	Capps	52	Female	Malignant
7.	Lattes*	32	Female	Benign
8.	Poppen & Riemenschneider*	26	Female	Malignant
9.	Proctor & Lindsay	55	Female	Malignant
10.	Winship, Klopp, & Jenkins	54	Female	Malignant
11.	Winship, Klopp, & Jenkins	64	Male	Benign

* To be published.

The following authors reported cases that appear to fulfill the clinical and histological requirements necessary to be considered as glomus-jugularis tumors: Robinson, Thorell, Bilancioni, Beck, Goekoop (three cases in one family), Guisez and Richez, Fraser two cases), Manasse, Ormerod, and Bryant.

In addition, there are reported cases which probably should be classified as glomus-jugularis tumors by Junod, by Bronzini, and by Urbantschitsch. The latter, writing in 1913, described a 76-year-old woman who had a middle-car tumor diagnosed as angiosarcoma. Because of frequent hemorrhages, this was treated by continuous lemon juice to the tumor, which, the author stated, prevented bleeding by thrombosis of peripheral capillaries.

No attempt is made to review all the literature on middle-ear tumors, for it was found impossible to reach any definite conclusions as to the actual diagnosis in many suggestive cases, owing to the lack of photomicrographs and the inadequate record of operative and microscopic findings, especially in the older literature. Suffice it to say that an incomplete review of the literature on primary middle-ear tumors shows a fair number of acceptable glomus-jugularis tumors. These are shown in Table 2.

Clinical History

Clinically these cases show a marked similarity. The tumor manifests itself most frequently between the ages of 45 and 50 years, although Bilancioni's case occurred in a 5-year-old girl, and the tumor reported by Robinson was obtained from a man 78 years old. All patients give a long history, the most common symptoms being:

(1) Presence of an aural polyp which if ulcerated or removed bleeds profusely and tends to recur

(2) Loss of hearing progressing to deafness

(3) Chronic otorrhea

(4) Facial paralysis

(5) Pain, which is usually a late manifestation and may not be present if the tumor is benign.

The right and left ears seem to be involved with equal frequency as might be expected by the results of Guild's investigation. The tumors studied occurred more frequently in women than in men, there being nine proved cases in women and two in men; and nine probable cases in women and four in men.

On physical examination, most authors record a dark-red or purplish, soft, polypoid mass that appears to arise in the middle car and usually, but not always, extends into the external auditory meatus. These tumors have a tendency to spread by contiguity and to destroy adjacent bone. This occurs not only in the malignant tumors by invasion, but also in long-standing benign tumors where it is apparently caused by pressure necrosis. The clinical course of this growth is similar to that of carotid-body tumors which, when malignant, usually cause death by erosion through the temporal bone into the brain. More frequent, widespread invasion of other adjacent structures should be expected from a malignant tumor in this location. To explain the localization of bone destruction in these cases, it is suggested that temporal-bone invasion in the presence of a malignant carotid-body tumor may actually be an extension from a concurrent homolateral malignant glomus-jugularis tumor.

Table 2

CASES OF PROBABLE GLOMUS-JUGULARIS TUMORS

No.	*Author*	*Age*	*Sex*
1.	Robinson	78	Male
2.	Thorell	42	Male
3.	Bilancioni	5	Female
4.	Beck	23	Female
5.	Goekoop	21	Female
6.	Goekoop	19	Female
7.	Goekoop	25	Female
8.	Guisez & Richez	64	Female
9.	Fraser	62	Female
10.	Fraser	47	Female
11.	Manassee	55	Male
12.	Ormerod	51	Female
13.	Bryant	41	Male

Metastases from glomus-jugularis tumors are as rare as those from carotid-body tumors. Case 1 is the only one reported that actually showed the presence of metastasis, which occurred in an upper jugular lymph node.

The life history of the disease is such that few alarming symptoms are apparent until

late, when complete removal becomes difficult or impossible. Hemorrhage at the time of operation is profuse and usually difficult to control. The explanation is obvious both on microscopic examination, when the rich vascular nature of the tumor is observed, and on anatomical examination when its intimate relation to the jugular bulb is evident. The difficulty in hemorrhage could perhaps be partially eliminated by ligation of the external carotid artery, since the glomus jugularis is supplied by its ascending pharyngeal branch.

Adequate exposure allowing complete removal of the tumor is essential, for benign and malignant variants are indistinguishable grossly, and frozen-section estimates would be difficult. Theoretically it is possible to remove a malignant glomus-jugularis tumor completely but, because of its anatomical location, not without damage to the jugular vein. This, however, does not appear to be too serious a complication if one can judge by Dr. Jenkins' case.

Close postoperative follow-up over a long period is indicated to detect recurrence and avoid irreparable damage to the temporal bone. Awareness of the potentialities of such tumors is important, because regional destruction and metastases occur late, and any opportunity for a cure lies in early diagnosis and radical removal of the entire tumor. No beneficial results have been seen from irradiation in the two cases of malignant glomus-jugularis tumor, in this series, that have received known dosage.

Summary

Two cases of glomus-jugularis tumor are described, one of which is malignant and has metastasized. All known cases of glomus-jugularis tumor have been reviewed as well as all available cases previously diagnosed as endotheliomas and hemangioendotheliomas. In all, eleven cases are accepted as belonging in the category of glomus-jugularis tumor. An incomplete review of the literature on middle-ear tumors suggests that others could be classified with this group. A histological comparison has been made between the collected cases of tumor and Guild's sections of normal glomus jugularis. This tumor should be considered in the differential diagnosis of patients presenting aural polyps, chronic otorrhea, deafness, facial paralysis, or bone destruction in the region of the middle ear. Malignant glomus-jugularis tumors appear to be radioresistant.

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RESECTION OF STOMACH AND ADJACENT ORGANS IN CONTINUITY FOR ADVANCED CANCER

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IN the not too distant past, a famous surgeon said that he who would operate for gastric cancer was responsible for two fatalities at a single stroke—the patient and his own surgical reputation. During the intervening years, progress in the training of surgeons, advances in anesthesiology, and a more complete understanding of the principles of nutrition have so reduced the hazard of operations on the stomach that the operative mortality for such procedures is now quite low. In many surgical clinics, total gastrectomy and resection of the gastric cardia are carried out routinely whenever indicated. The successful end results have justified the perseverance with which these tedious operations have been performed. In a recent analysis of seventy-five survivors of subtotal gastrectomy for cancer at Memorial Hospital, 34 per cent had lived for five years without recurrence. When the case histories of these patients are closely scrutinized and the operative procedures recalled to mind, one can not fail to be impressed with the fact that many of the patients, who have been free of recurrence or metastasis for years, presented problems at the operating table that were, at the time, almost sufficient to induce the surgeon to terminate the operation at once.

Even now, gastric cancers that are found to be fused with the transverse colon, the left lobe of the liver, the pancreas, the dia-

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FIG. 1. *Resection. Gastric cancer infiltrating the transverse colon. Case 1.*

FIG. 2. *Resection. Cancer of the transverse colon infiltrating the stomach. Patient survived eight years. Case 5.*

phragm, the abdominal wall, or the spleen, either through direct invasion by the primary tumor or indirectly by metastatic lymph nodes, offer a real challenge to the surgeon. At the time he may often wish that he had left well enough alone, and wonder whether the end results will justify the means. That such operations are fully warranted, in the absence of distant metastases to the liver, peritoneum, mesentery, or other organs, is well illustrated by the results obtained in the small series of cases presented here. Such extensive resections are to be deplored if distant metastases are present, or if done for purely palliative purposes, unless there is some very strongly specific indication. If the clearly defined purpose is curative, then any procedure is warranted that has a reasonable chance of success and will leave the patient in an improved condition. Thus, six of the fifteen case reports which form the basis for this discussion deal with patients treated prior to 1943. Four are living and well, engaged in active lives, and free of recurrence or metastases for periods ranging from five to ten years (see Table 1). It is reasonable to suppose that a fair percentage of the more recently treated patients will survive for a number of years.

As the experience of surgeons increases, and progress in the understanding of supportive measures and nutrition continues, it is not unlikely that massive resections of the stomach and adjacent viscera will be reported

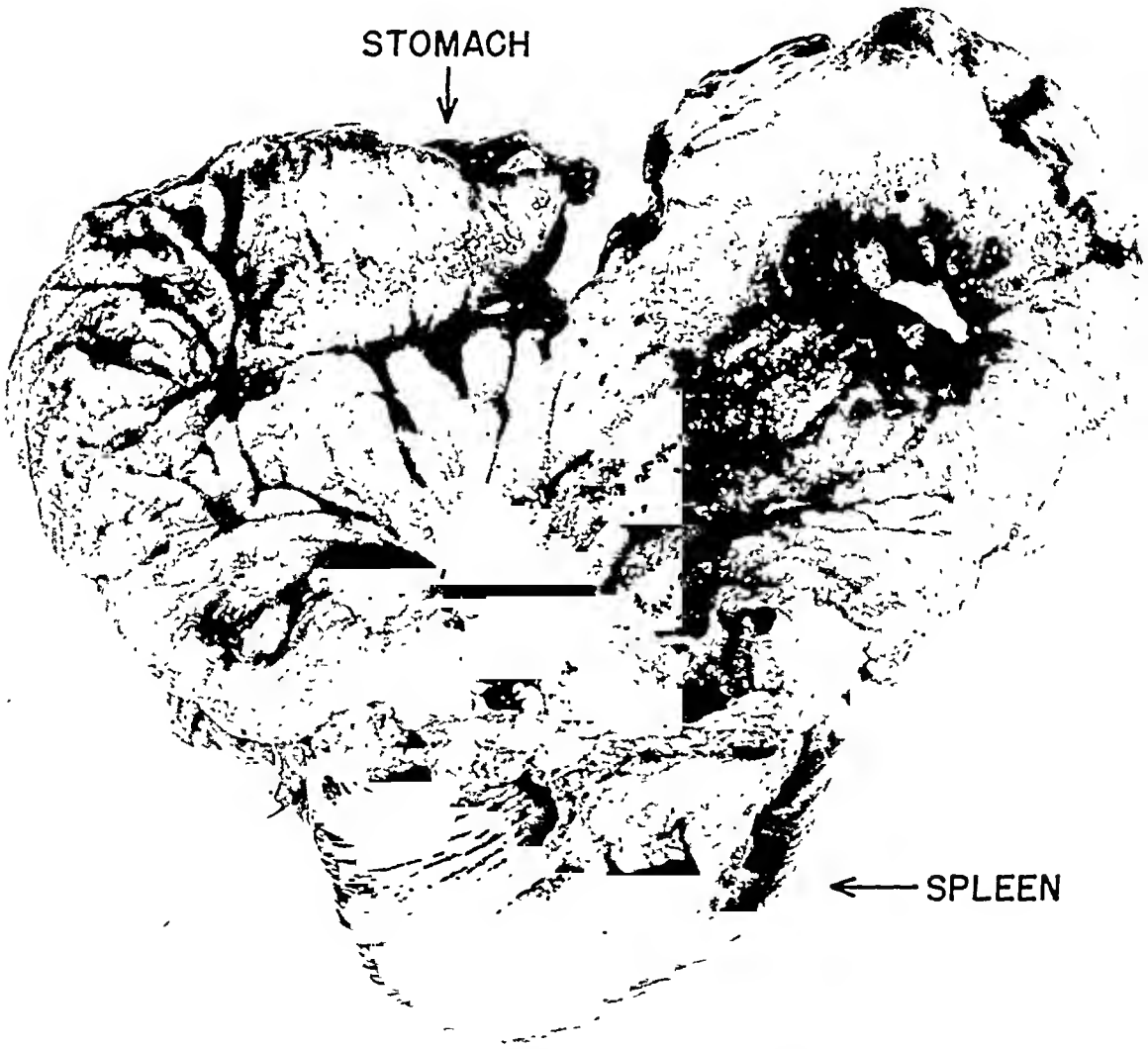

FIG. 3. *Resection of gastric cardia, spleen, tail of the pancreas, part of the attached liver. Anterior view, demonstrating ulceration into the spleen. Case 11.*

in ever-increasing numbers. Until the cause and cure of cancer are finally brought to light, the only obstacle to deter the surgeon from attempting to resect gastric cancers should be distant metastasis or involvement of the fundamental blood supply, i.e., of the hepatic artery, the superior mesenteric vessels, and the aorta.

Material

This deals with patients, treated at the Memorial Hospital from 1932 to 1947, in whom at least part of the stomach and one or more other organs or parts of organs have been resected. Cases in which the greater omentum only was resected together with the stomach are not included because that organ is routinely removed in all subtotal or total gastrectomies for cancer; neither are those in which total gastrectomy alone or cardiectomy alone was performed.

Surgery Performed

The surgical procedures followed (Table 1) depended upon the findings. In six patients, subtotal gastrectomy and partial resection of the transverse colon was done, accompanied by a Mikulicz-type procedure on the latter. A double-barrel colostomy was constructed and closed at a later date. In four of the patients, subtotal gastrectomy was performed in conjunction with partial excision of the pancreas. In case 6, the liver, bearing tumor by direct extension, was excised by cautery. In case 10, that portion of the stomach containing the tumor was removed in continuity with the invaded abdominal wall. In case 11, partial gastrectomy was combined with splenectomy and partial resection of the pancreas and liver. In case 14, a portion of the left lobe of the liver, fixed to the stomach by a perforated carcinomatous ulcer, was resected in continuity with the gastric tumor. In case 15, the problem required total gastrectomy plus splenectomy.

Pathological Findings

In two instances supposedly malignant ulcerated lesions were found to be benign on microscopic study of the specimens. In ten others, a diagnosis of adenocarcinoma was established histologically. Metastatic cancer was present in the lymph nodes accompanying five specimens.

Fig. 4. *Resection of the gastric cardia, spleen, tail of the pancreas, and part of the attached liver. Posterior view. Case 11.*

Patients Surviving Operation Five or More Years Without Recurrence

Case 1. S.F., a 67-year-old man, first came to Memorial Hospital, May 4, 1942, complaining of epigastric distress and vomiting of four to five months' duration, and a 30-pound loss of weight. Physical examination revealed a hard irregular mass lying directly beneath the abdominal wall in the left epigastrium. This could be seen to move on respiration. Gastric analysis showed a free HCl of twenty-eight degrees. Fluoroscopy after barium meal revealed an epigastric mass, corresponding to a fusiform defect, involving the

TABLE 1

RESECTION OF STOMACH AND ADJACENT ORGANS IN CONTINUITY

Case number	Date of operation	Operative findings	Operative procedure	Pathological findings	End result
			Patients Operated Upon Prior to 1943		
1. S.F.	5/16/42	Large tumor in mid-third of stomach involving the colon	Partial gastrectomy. Partial resection of transverse colon	Adenocarcinoma gr. II involving all layers	Living and well 5 yrs., 3 mos.
2. J.B.	6/5/40	Tumor involving mid-portion of stomach. Adherent to tail of pancreas	Partial gastrectomy. Partial resection of pancreas	Adenocarcinoma gr. III	Living and well 7 yrs., 2 mos.
3. W.H.	9/16/32	Pylorus, antrum, and pars media involved. Nodes near middle colic artery	Partial gastrectomy. Partial resection of pancreas	Diffuse small-cell carcinoma gr. IV, metastatic to nodes	Operative death
4. S.R.	3/13/39	Indurated mass in distal stomach extending into head of pancreas	Partial gastrectomy. Partial resection of head of pancreas	Deeply infiltrating adenocarcinoma gr. II	Survived 15 mos.
5. M.M.	4/10/39	15 × 20 cm. mass originating in transverse colon, invading stomach	Partial gastrectomy. Partial resection of transverse colon	Adenocarcinoma of colon perforating into stomach	Living and well 7 yrs., 4 mos.
6. L.P.	6/7/37	Massive tumor involving pylorus and invading liver	Partial gastrectomy. Cautery excision of left lobe of liver	Papillary and infiltrative adenocarcinoma gr. II, invading lymph nodes	Living and well 10 yrs.
			Patients Operated Upon after 1942		
7. A.U.	3/15/43	Mass originating in antrum of stomach. Attached to posterior wall of transverse colon	Resection of two-thirds of stomach. Partial resection of trans. colon and trans. mesocolon	Adenoma malignum gr. I, metastatic to nodes along lesser curvature	Survived 3 yrs. 1 mo.
8. J.L.	2/1/45	Infiltrating tumor in pre-pyloric area on greater curvature. Invasion of transverse colon	Partial gastrectomy. Partial resection of transverse colon	Adenocarcinoma gr. IV extending through serosa into transverse colon	Living and well 12 mos.
9. M.E.	6/14/45	Bulky tumor in distal stomach infiltrating pancreas and adherent to liver	Partial gastrectomy. Partial resection of pancreas	Adenocarcinoma gr. III invading pancreas, metastatic to nodes	Operative death
10. S.L.	10/20/43	Tumor in stomach. Adherent to abdominal wall	Partial gastrectomy. Resection of involved abdominal wall	Adenocarcinoma gr. III	Survived 1 mo.
11. J.M.	8/19/46	Penetration of ulcer into liver, pancreas, and spleen	Cardiectomy. Partial resection of pancreas and liver. Splenectomy	Multiple peptic ulcers penetrating spleen, pancreas, and liver	Living and well 11 mos.
12. S.S.	7/19/46	Mass on greater curvature, extending into transverse mesocolon	Partial gastrectomy. Partial resection of transverse colon	Adenocarcinoma gr. III extending into serosa of colon	Living and well 13 mos.
13. S.K.	9/3/46	Gastric ulcer penetrating into pancreas	Partial gastrectomy. Partial resection of pancreas	Chronic peptic ulcer penetrating into pancreas	Operative death
14. J.R.	4/2/46	6 cm. stomach mass fused with liver-abscess walls	Partial gastrectomy. Cautery excision of liver abscess	Adenocarcinoma gr. III	Survived 7 mos.
15. I.M.	7/31/46	Tumor of greater curvature attached to spleen	Total gastrectomy. Splenectomy	Adenocarcinoma gr. IV, metastatic to nodes	Operative death

distal half of the stomach, principally along the lesser curvature.

Upon exploration on May 16, 1942, a large tumor of the lower third of the stomach was found. It was quite movable, but involved the mesocolon and obliterated the lesser omental cavity at this point. The entire omentum was dissected free from the anterior-superior surface of the transverse colon. It was found impossible to dissect the tumor mass without compromising the middle colic artery. This was therefore ligated, and the entire thickness of the mesocolon transected around the tumor. Subtotal gastrectomy was performed in the usual manner employing a retrocolic antiperistaltic anastomosis of stomach and jejunum of the Hofmeister type. The transverse colon was then examined and was found to be quite cyanotic and of questionable viability. An obstructive type resection of the involved colon was carried out employing a Rankin clamp. The two loops of transverse colon were next exteriorized through the incision.

The pathological diagnosis was adenocarcinoma, grade III.

Closure of the colostomy was effected on June 28, 1943.

The patient was last seen and found to be in excellent health on August 20, 1947.

Case 2. J. B., a 52-year-old man, entered Memorial Hospital, June 2, 1940, complaining mainly of abdominal pain. He had had some upper abdominal discomfort for the previous three years. Four months prior to admission, he complained of pain that radiated from the epigastrium to the back and chest, associated with nausea and vomiting. Some relief was afforded by powders prescribed by his physician. Advanced anemia and cachexia were evident upon physical examination. An abdominal mass was not palpable, although there was tenderness in the epigastrium. A series of gastrointestinal roentgenograms showed a constant filling defect in the pars media, consistent with carcinoma of the stomach. These findings were confirmed by gastroscopy.

On June 5, 1940, the abdomen was explored. A tumor was palpated in the posterior wall of the stomach, partially fixed to the tail of the pancreas. The stomach was then freed of its attachments to liver and colon, and the duodenum divided and closed in the usual manner. When the stomach had been reflected to the left and anteriorly, it was seen that the gastric tumor was densely adherent to the tail of the pancreas. Routine subtotal gastrectomy was then performed. A portion of the pancreas was removed with the actual cautery in continuity with the gastric tumor.

Pathological diagnosis was adenocarcinoma, grade III.

The patient has remained free of disease until the time of this report, seven years postoperatively.

Case 3. M. M., a 65-year-old woman was first seen at the Memorial Hospital, April 6, 1939, complaining of abdominal tenderness, nausea, and vomiting. In June, 1938, she had been operated upon at another hospital and was told she had an inoperable intra-abdominal cancer. Physical examination revealed a patient in good general physical condition. There was a hard, movable mass, the size of a grapefruit, in the epigastrium. Laboratory investigation revealed a mild anemia. Roentgenograms following barium enema demonstrated a filling defect in the proximal end of the transverse colon suggesting carcinoma.

On April 10, 1939, she was subjected to a surgical exploration, at which time a mass roughly 15 to 20 cm. in diameter was found in the mid-portion of the transverse colon, attached to the greater curvature of the stomach. A portion of small bowel adherent to the tumor was dissected free. After the mesocolon had been transected on either side of the process, a Rankin clamp was applied to the two loops of colon and a Payer clamp placed across the greater curvature of the stomach, so that the transverse colon including the tumor together with the involved stomach was removed en bloc. The stomach defect was closed in two layers and a double-barrel colostomy established as the abdomen was closed.

Pathological diagnosis was adenocarcinoma of colon perforating the stomach.

The postoperative course was uneventful. The colostomy was closed on October 13, 1939. The patient has remained well eight years after operation.

Case 4. L. P., a 58-year-old man was admitted to Memorial Hospital on June 1, 1937. At that time, he complained of attacks of indigestion and nausea, recurring at irregular intervals for the previous six years. Two years before admission, he began having periods of epigastric pain, definitely relieved by ingestion of food. Physical examination revealed a poorly nourished white male. A mass could not be palpated in the epigastrium. Gastric analysis showed 21 degrees of free HCl. There was marked anemia. A series of gastrointestinal roentgenograms revealed a large tumor that projected from the greater curvature of the stomach, suggesting carcinoma.

On June 7, 1937, the abdomen was explored. A massive tumor occupying the pyloric end of the stomach was found, with numerous nodes along the lesser and greater curvatures. There was direct extension of the growth on the lesser curvature of the stomach to the under surface of the liver. The entire process was removed en bloc, by resection of a major portion of the left lobe of liver, in association with subtotal gastrectomy.

Pathological diagnosis was papillary and infiltrative adenocarcinoma grade II with metastasis to accompanying lymph nodes.

The patient has remained free of recurrence and in excellent health for more than ten years.

Summary

The case histories of four long-term survivors are reported in whom subtotal or total gastrectomy was performed in conjunction with resection of a part or all of one or more other adjacent abdominal organs. These and eleven additional recent cases are summarized in tabular form. In the main, the operations were performed for carcinoma of the stomach. There are two cases of benign ulcer of the stomach and one case of carcinoma of the transverse colon included in the series.

End Results

This series of cases is small and about one-half of the operations have been performed since 1945. Six patients underwent operation prior to 1943. Four have been free of recurrence for more than five years. Of these four, the lymph nodes were found to be free of metastasis in three instances, and involved in one. An explanation of the long survival period and apparent cure in these patients may lie in the wider removal of adjacent tissues and lymph channels made possible by such extensive resections en bloc.

The Histamine Content of Neoplastic Pulmonary Tissues

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THE mechanism by which histamine is stored in and released from various tissues of the human body is a matter of considerable interest and importance not only to the physiologist but to the clinician. This potent agent, significant concentrations of which are present in lung, liver, gastrointestinal mucosa, kidney, spleen, and skin, has been implicated in a number of physiological and pathological reactions. These include Lewis' "triple response,"[31] the gastric phase of gastric secretion,[5] contractions of the gravid uterus,[18] toxemia of pregnancy,[4, 20] the disease called "stripper's asthma,"[19] glaucoma associated with epidemic dropsy,[8] severe unilateral headaches associated with rhinorrhea and tearing,[22] various allergic manifestations,[23, 35] traumatic shock,[6, 21, 34, 36, 39] anaphylactic shock,[9, 10, 12] and certain symptoms of snake poisoning.[13, 35]

One can attribute the formation of histamine to the decarboxylation of histidine. A histidine decarboxylase has been found in many tissues of the body,[29] and the contents of the gastrointestinal tract are rich in both histidine and histamine. Whether histamine is formed from histidine in the gastrointestinal tract to be absorbed and distributed to various tissues of the body, or whether decarboxylase in individual organs forms histamine from histidine at the point of storage is as yet unclear. It is probable that histamine is fixed in the "lipoprotein framework"[12] of the cell in conjugation with an amino acid which makes it pharmacologically inactive.[37] This linkage is believed to be in the form of a peptide and can be broken by acid hydrolysis or by the activity of proteolytic enzymes within the cell.[10, 37] The activation of proteolytic enzymes as an essential part of anaphylaxis may liberate histamine during the antigen-antibody reaction through the action of activated intracellular cathepsins.[37] In addition to the liberation of histamine by the action of tryptic digest, or by antigen-antibody reaction, its liberation may also be the function of special "histaminergic" neurones.[30, 33]

The histamine present in lung tissue has come under particularly close scrutiny, partly because of the high concentration and partly because of the lung's adaptability to perfusion experiments and to experimental resection.

Histamine appears to be released from lung tissue following numerous types of injury. Release of histamine from excised lung in vitro or from lung in vivo has been reported after perfusion with distilled water,[9] after anaphylactic shock,[9] after injections of staphylococcal toxins in the guinea-pig and cat lung,[14] after exposure of the dog lung to radiant energy,[24] after perfusion of guinea-pig and cat lungs with snake venom,[13] after exposure of dog lungs to high concentrations of volatile anesthetics,[25] and after injection of *Clostridium welchii* type-B toxin in the cat lung.[27] On the other hand there has been found to be no significant release of histamine from the living dog's lung "in vivo" after exposure to high concentrations of phosgene gas,[16] after the production of severe pneumococcal pneumonia,[15] the injection of *Cl. welchii* type-A toxin into the cat's lung,[26] or the long-term deprivation of pulmonary arterial blood.[16]

Simmonds, in 1941, showed that there was an almost complete absence of extractable histamine in the infant lung. In 1942, Bloomer attempted to correlate the histamine content of the lung, liver, kidney, spleen, mucosa of stomach, duodenum, and ileum with pathological lesions found in a series of nineteen autopsies. No significant

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TABLE 1

HISTAMINE CONTENT OF PRIMARY PULMONARY TUMORS

HISTAMINE IN γ/GM.

Type of tumor	Surgical Path. No.	Tumor Tissue			Lung Tissue			Tumor histamine in % lung histamine
		Observed readings		Average	Observed readings		Average	
Epidermoid carcinoma	39110	2	4	3	7	9	8	38
	39720	10	12	11	65	85	75	15
	39866	8	8	8	28	28	28	29
	40300	< 0.06	< 0.06	0	150	200	175	0
	40953	18	21	20	85	85	85	24
	41132	0.43	8	4	40	*	40	10
	41503	8	12	10	90	100	95	11
	41554	15	17	16	55	56	56	29
	41754	21	25	23	100	100	100	23
Average				11			74	15
Adenocarcinoma								
	40055	9	19	14	76	90	83	17
	41523	6	7	7	55	77	66	11
	41815	8	60	34	250	263	257	13
	41853	250	275	263	42	170	106	248
	42171	40	40	40	110	110	110	36
	41163	13	†	13	—	—	—	—
Average				62			124	50
Anaplastic carcinoma	38569	6						
	40675	< 0.13	7	7	100	125	113	6
	41337	13	< 0.13	0	71	71	71	0
			18	16	50	50	50	32
Average				8			78	13
Bronchial rest tumor	40056	240	260	250	—	—	—	—
Bronchial adenoma	40157	6	6	6	90	90	90	7

* Specimen lost.

† Biopsy specimen with insufficient material for duplicate analysis.

correlation was found in this short series with its limited variety of pathological lesions.

Since the lung is a rich source of extractable histamine, it seemed to us worth while to investigate whether neoplastic tissue presumably derived from bronchial mucosa would also contain a high concentration of histamine and whether there would be significant differences with varying histological types of tumors. For this purpose, fresh, surgically excised specimens were subjected to bioassay of both neoplastic tissue and uninvolved lung tissue.

Procedure

Between July, 1946, and September, 1947, tissue blocks were removed from all surgical lung-tumor specimens, from the thoracic service of the New Haven Hospital, when sufficient neoplastic tissue was available for histamine assay in addition to routine microscopical examination. The specimens were obtained shortly after removal of the lung and always within two hours. Blocks of adjacent normal-appearing lung as well as a representative specimen of the tumor tissue were taken except in three instances where only a local excision had been carried out and control lung tissue was not obtainable.

The blocks varied from 0.5 to 2.5 gm. After blotting off all excess blood and moisture, the blocks were weighed in duplicate to the nearest hundredth of a gram. The extraction then proceeded according to a method described by Gilman and Lindskog.[15] The tissue was first ground with white sand until fragmentation seemed complete, the mixture then transferred to wide-mouthed bottles. Forty ml. of 70% alcohol containing enough hydrochloric acid to make a 0.1 N solution was added, and the mixture was shaken mechanically for three hours. Following this the contents of each bottle was transferred to a 50 cc. tube and centrifuged for five minutes at high speed. The supernatant solution was poured into a porcelain evaporating dish, and the centrifugation repeated after adding 20-30 cc. of the alcohol to the sediment and stirring well. The solutions were evaporated on a steam bath and the dried residues were set aside until a convenient time for assay.

Assay Method

The dried extract was dissolved in Tyrode's solution so that 5 ml. corresponded to 1 gm. of the original lung or tumor tissue.

Assay was done according to a modification of the method described by Guggenheim and Löffler. Test strips of about 2 cm. of the distal ileum of a young, freshly killed guinea pig were used, the contents of which were immediately washed out with Tyrode's solution. A strip of gut was then attached to the measuring apparatus, one end being fastened to a stationary hook at the bottom of a container and the free superior end suspended by a thread from a writing lever. The usual measurement and recording of contractions on a smoked drum were replaced by direct readings from a millimeter scale fixed in the arc of the writing lever point.

The test strip of ileum thus prepared was immersed in 3 cc. of Tyrode's solution, (to which had been added 1 gm. of glucose and 1 mg. of atropine per liter). The use of redistilled water for the Tyrode's solution was found to double the time period over which effective contractions could be expected from a single gut specimen.

To the immersion fluid was added a proper amount of dissolved extract to be tested so that contractions within an optimum range were produced. These contractions were then compared with those produced by standard histamine solutions. The quantities of the unknown extract in solution and the standard used for comparison were kept nearly equal in volume to avoid dilution errors. Immediately after evaluation of a response, the solution bathing the gut strip was replaced with fresh Tyrode's solution. The bath was kept at a constant temperature of 37° C.

Results

A total of twenty primary lung tumors were analyzed for their histamine content. Control analyses of the uninvolved lung from the same cases were obtained in all but three. Included were eighteen carcinomas, one bronchial adenoma, and one bronchial rest tumor. The carcinoma group was further subdivided into epidermoid (nine specimens), adenocarcin-

oma (six specimens), and anaplastic (three specimens).

In Table 1 the tumors are grouped according to this histological classification. Histamine values are recorded for the observed readings of duplicate samples together with the mean. In the last column the per cent histamine content of the tumor is stated relative to the content in the normal-appearing or control tissue from the same lung.

In the epidermoid group of nine, the histamine content of tumor tissue ranged from 3 to 20 γ per gm. with an average of 11 γ per gm. Thus the tumors in this group contained from 0 to 38 (av. 15) per cent of the histamine present in the lung itself.

In the adenocarcinoma cases the histamine content of the tumor tissue ranged from 7 to 263 γ per gm. with an average of 62 γ per gm., whereas the histamine of the control tissue for this group ranged from 66 to 257 γ per gm. with an average of 124 γ per gm. One of these cases did not have controls, for only biopsy of the lung was done. Taking this group as a whole the average tumor contained 50 per cent of the histamine to be found in the normal tissue.

In the anaplastic carcinoma group, the tumor-tissue histamine ranged from less than 0.13 to 16 γ per gm., with an average of 8 γ per gm. That of the control lung tissue was 50 to 113 γ per gm., with an average of 78 γ per gm. This group had the least concentration as compared with the normal lung, the average being 13 per cent.

Tissues from two benign tumors were available for this analysis. One of these was a peripheral bronchial rest tumor of the right middle lobe. It showed the remarkably high histamine content of 250 γ per gm. Unfortunately, no control tissue was obtained. The second, a typical bronchial adenoma, contained 6 γ per gm., which was 7 per cent of that found in the accompanying normal lung.

Discussion

The results demonstrate a decreased content of extractable histamine in neoplastic pulmonary tissue. Three possible explanations for this phenomenon are suggested. It has been shown that fetal lung tissue is especially low or wanting in extractable histamine.[38] The low content in neoplastic tissue may represent a reversion of growth and biochemical characteristics toward those of embryonal lung tissue. A second possibility is that the histamine in lung is found largely in stromal cells not present in great abundance in the tumors, which consisted primarily of epithelial derivatives. Third, neoplastic lung tissue may be especially rich in histaminase, a possibility that deserves to be investigated further.

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STUDIES ON INVASIVENESS OF CANCER

*Adhesiveness of Malignant Cells in Various Human Adenocarcinomas**

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IN RECENT papers [2, 3, 4] from this laboratory on the mechanisms of invasiveness in cancer, evidence was presented that squamous-cell cancers owe their ability to spread through tissues, in part, to decreased cellular adhesiveness. By means of a quantitative method, it was shown that, as compared with normal cells, less force is required to separate pairs of opposed cancer cells.[2] Since only squamous-cell carcinomas were investigated, it seemed desirable to extend the study to glandular cancers, in order to find out whether decrease in adhesiveness is characteristic of carcinoma cells generally.

MATERIAL AND METHODS

Because of technical difficulties, the adhesiveness of cells from glandular carcinomas could not be conveniently measured by the method used with squamous-cell carcinomas, that is, by pulling apart pairs of attached cells with microdissection needles. Instead, a shaking device was used; cancer tissue and normal tissue were separately immersed in fluid and shaken simultaneously under identical conditions. The intensity of shaking was so regulated as to dislodge from the tissues and to separate from each other those cells less strongly bound together, while more firmly bound cells remained attached. In order to compare the effects of shaking on malignant and normal tissues, cell counts were made at intervals during the procedure, and, at the end of the experiment, histological sections were prepared to show to what extent the epithelial cells had been dislodged.

A Boerner shaker was employed. This instrument is provided with two upright bars, to one of which were attached two 100 cc. flasks, each containing 5 cc. of a balanced saline solution (Gey's). Cancer tissue was placed in one flask, normal tissue in the other. To the second upright was attached another 100 cc. flask as counterbalance. On both uprights, the positions of the flasks were adjusted to obtain maximal intensity of shaking. In order to obtain lesser intensities, the weight of the counterbalancing flask was altered by placing various amounts of water in it. In this way, four intensities of shaking were obtained empirically, which were reflected in four degrees of turbulence of the fluid in the tissue-containing flasks.

Experiments were made as follows: Human tissues were obtained as soon as possible after surgical removal, kept dry in an ordinary refrigerator, and tested within a few hours. Pieces of nearly equal size were cut from the cancerous tissue and from the supposedly normal tissue outside the cancerous area. The size of the pieces varied somewhat but measured approximately 1 × 1 × 0.2 cm. Each piece of tissue was placed in one of the flasks on the shaker and was immersed in 5 cc. of the balanced salt solution. The shaker was adjusted to produce the first (lowest) degree of turbulence and run for fifteen minutes. The fluid in which tissues were immersed was removed, and cell counts made in a counting chamber, comparing the number of cells shaken from cancerous tissue with the cells dislodged from normal tissue. As the cells were sometimes distorted or broken as the result of shaking, it was at times difficult to identify the cell type. Therefore it was made the rule to count all single, that is to say, separated cells (except leukocytes) in which both nucleus and cytoplasm were rec-

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FIG. 1. *Unshaken tissue from cystic disease of the breast.*

FIG. 2. *Tissue from cystic disease of the breast, after it was shaken.*

FIG. 3. *Tissue from carcinoma of the breast, unshaken.*

FIG. 4. *Tissue from carcinoma of the breast after being shaken.*

Note practically complete loss of cells from carcinomatous tissue as result of shaking, in contrast to retention of cells in cystic disease.

ognizable, even if the cytoplasm were not completely intact. Naked nuclei, however, were not counted, nor were attached pairs and clumps of cells, since their presence would give no indication of their adhesiveness.

After the tissues were shaken as described, the machine was adjusted for the second, third, and fourth degrees of turbulence successively; the tissues were agitated fifteen minutes at each turbulenee, and cell counts made after each shaking.

At the conelusion of the experiment, the shaken tissues were fixed in formalin, and sections prepared and stained with hematoxylin and eosin. Photomicrographs were made of representative fields, care being taken that the photograph should include an edge of the tissue, since deeply located cells could not be expected to eseape easily, especially from tissues having a dense stroma. Also, photographs were made of sections from comparable blocks of tissue that had not been shaken.

In this way it was possible to compare the cellular content of the tissues before and after shaking and to compare the effect of agitation upon the cellular content of the normal tissue and its neoplastic derivative.

Whereas the cell counts showed the number of single cells dislodged, the photomicrographs revealed the cells still remaining in the tissue.

Results

In Table 1, in a representative experiment, it is seen that more separate cells were dislodged from cancerous than from normal tissue. Most of the cells from the cancer came out during the first fifteen-minute period, while most cells from the normal tissue were dislodged during the last and most intense period of agitation.

Table 1
A REPRESENTATIVE EXPERIMENT
The Numbers of Single Cells Dislodged from Cancerous and Corresponding Normal Tissues During Four 15-Minute Periods of Agitation of Increasing Intensity

Turbulence	*Carcinoma of colon cells/ cu. mm.*	*Normal colon cells/cu. mm.*
1	6240	70
2	190	80
3	10	130
4	0	600
TOTAL	6440	880

In Table 2 are given data on twenty-one experiments. The cell counts represent the totals from the first three periods of agitation. In all but two experiments (numbers 4 and 13), more cells were dislodged from the cancerous than from the normal tissue; and in one of these two cases (number 13), examination of photomicrographs showed that the eells dislodged from the "normal" tissue were exudative cells from a pneumonie lung rather than cells of the lung tissue itself. In the right-hand column of Table 2 are given, in plus signs from + to ++++, the numbers of cells dislodged and separated from tissues, estimated by comparing photomicrographs of shaken and of unshaken tissues. Judging by the empty spaces in shaken tissues, more cells were dislodged from cancers than from noncancerous tissue in all but one experiment (number 4), and there is seen to be good correlation between the results as judged by cell counts and by photomicrographs.

In order to illustrate the different effects of agitation on cancerous and noncancerous tissues, photomicrographs from four representative experiments are shown in Figs. 1 to 16. In the first plate (eystic disease of the breast and carcinoma in the same breast), Fig. 2 shows that while some of the hyperplastie epithelium has been detached from its basement membrane as a result of shaking, the epithelial cells remain attached to one another, in strands or clumps, giving evidenee that their mutual adhesiveness was able to resist the disruptive force of agitation. In the carcinoma (Figs. 3 and 4), by contrast, praetically all the cancer cells have been displaced, even from the depth of the tissue, leaving only stroma.

Also in the earcinoma of the thyroid (Figs. 7 and 8), the eancer was highly cellular, so that great masses of tumor cells were dislodged by agitation although a few were left in the deeper part of the tissue. But in nodular hyperplasia of the thyroid (from another individual) (Figs. 5 and 6), the epithelium

FIG. 5. *Unshaken tissue from nodular hyperplasia of thyroid.*

FIG. 6. *Tissue from nodular hyperplasia of the thyroid, after it was shaken, showing loss of colloid but retention of cells.*

FIG. 7. *Unshaken tissue from carcinoma of thyroid.*

FIG. 8. *Tissue from carcinoma of the thyroid after it was shaken, showing loss of colloid but retention of cells.*

was not even detached from its basement membrane although the colloid was thrown out.

In the cancer of the stomach represented in Figs. 11 and 12, the growth comprises a larger amount of stroma than occurred in the cancers previously illustrated; nevertheless, all the cancer cells have been dislodged from the superficial tissue, their former positions being now represented by empty spaces. In the deeper tissue, some cancer cells remain.

The contrast with normal stomach is great (Figs. 9 and 10). The normal tissue is much more cellular than is the cancer; neverthe-

TABLE 2

RESULTS OF SHAKING CANCEROUS AND NORMAL TISSUES
Relative Loss of Cells as Estimated from Cell Counts and from Photomicrographs

		Cells/cu. mm.	o–++++
1	Carcinoma of stomach	550	+++
	Normal stomach	150	+
2	Carcinoma of stomach	260	+++
	Normal stomach	200	+
3	Carcinoma of stomach	100	+++
	Normal stomach	50	+
4	Carcinoma of stomach	60	+
	Normal stomach	70	++
5	Carcinoma of sigmoid colon*	260	+++
	Normal sigmoid colon*	150	+
6	Carcinoma of sigmoid colon	1,330	+++
	Normal sigmoid colon	0	+
7	Mucoid carcinoma of colon	100	++++
	Normal colon	35	+
8	Carcinoma of rectum	40	+++
	Normal rectum	10	++
9	Carcinoma of rectum	9,700	+++
	Normal rectum	420	+
10	Carcinoma of rectum	1,700	++
	Normal rectum	280	+
11	Secondary carcinoma of lymph node*	31,000	+++
	Normal liver*	45	+
12	Secondary carcinoma of liver*	80	++++
	Normal liver*	50	o
13	Carcinoma of lung	50	+++
	Pneumonic lung	260†	o
14	Carcinoma of thyroid gland‡	—	+++
	Nodular hyperplasia of thyroid‡	—	+
	Nodular hyperplasia of thyroid‡	—	o
15	Carcinoma of breast	1,000	+++
	Normal breast	20	o
16	Carcinoma of breast	210	++
	Normal breast	4	o
17	Carcinoma of breast	900	+++
	Normal breast	20	o
18	Carcinoma of breast	210	+
	Normal breast	30	o
19	Carcinoma of breast	630	+++
	Normal breast	20	o
20	Carcinoma of breast	—	++++
	Normal breast	—	o
21	Carcinoma of breast	—	+++
	Cystic disease of breast	—	o

* From necropsy.
† Exudative cells.
‡ From different individuals.

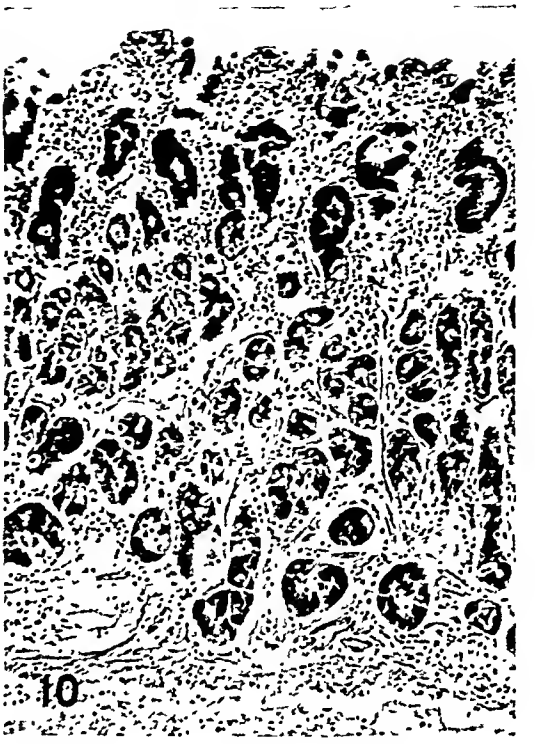
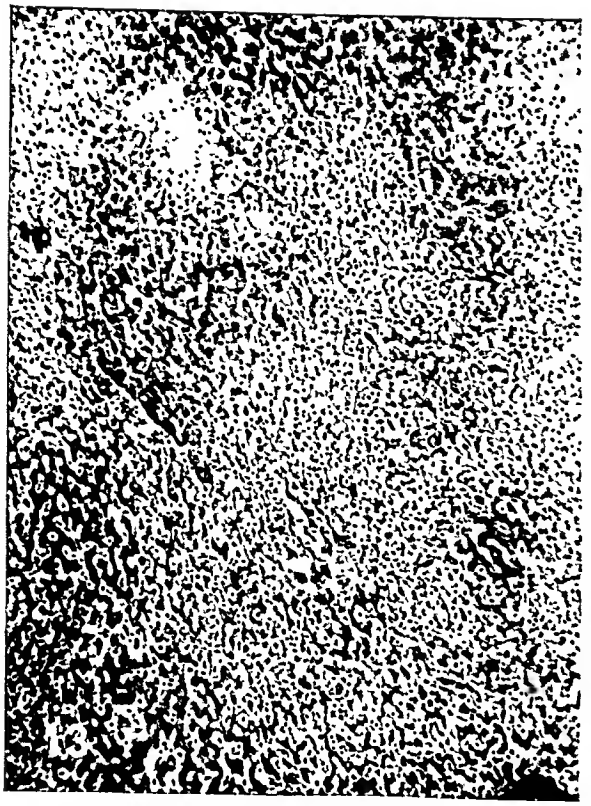


FIG. 9. *Unshaken tissue from normal stomach.*

FIG. 10. *Tissue from normal stomach, after it was shaken.*

FIG. 11. *Tissue from carcinoma of stomach, unshaken.*

FIG. 12. *Tissue from carcinoma of stomach after it was shaken, showing loss of many cancer cells.*



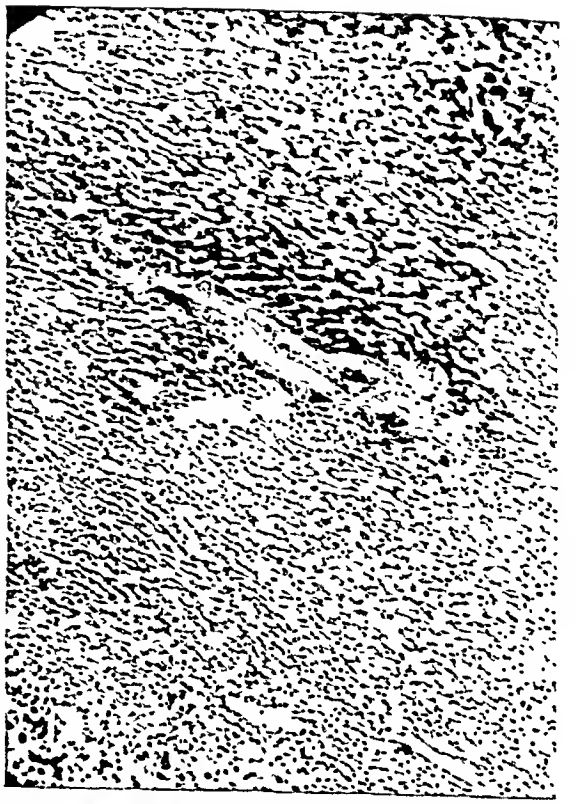


FIG. 13. *Normal liver tissue, unshaken.*

FIG. 14. *Normal liver tissue after it was shaken; shrinkage of liver cells without reduction in number.*

Fig. 15. *Section of liver containing metastatic carcinoma, unshaken.*

FIG. 16. *Metastatic carcinoma of liver after it was shaken. Nearly all the cancer cells have been dislodged.*

less, except for some cells lining the lumen of the stomach, the epithelium is intact.

It was thought of interest to study adhesiveness in a cancer that was metastatic, and accordingly Figs. 13 to 16 represent an intestinal carcinoma secondary in the liver. The material was obtained from an autopsy. As seen in Figs. 15 and 16, the cancer cells were largely dislodged, leaving empty spaces. The normal liver, in contrast, has apparently lost no cells through agitation, although the liver cells have shrunk in size, suggesting that the cohesiveness of their cytoplasm was less than the adhesiveness of the cell surface.

Discussion

The results of these experiments show that in twenty of twenty-one cases, cancer cells were not only dislodged by agitation to a greater extent than were normal cells, but the dislodged cells were more readily separated from one another. This information was obtained in part by comparing photomicrographs of shaken and unshaken normal and cancerous tissues. Large empty spaces in cancerous tissue after agitation left no doubt that, as compared with normal tissues, many more cells had been dislodged. However, it cannot be judged from photographs whether cells have been dislodged separately or in clumps (in the latter case, mutual adhesiveness of cells might still be high, although adhesiveness to the basement membrane were low). It was for this reason that cell counts were made on the fluid in which tissues had been shaken. Only single cells were enumerated, no cells in pairs or clumps being included in the counts. The fact that far more separate cancer cells than normal ones were found to have been dislodged gives evidence that the cancer cells were less firmly attached to one another.

Since the cells of human epidermoid cancers have already been shown to have reduced adhesiveness,[2] the conclusion seems justified that lessened adhesiveness is characteristic of human carcinoma cells generally. As glandular cancers are often highly invasive, the result here reported is consistent with the hypothesis that invasiveness of cancers is made possible by reduction in mutual adhesiveness of cancer cells.

As the consequence of this change, carcinoma cells are likely to become detached from aggregations of similar epithelial elements and, then, as separate cells, to penetrate surrounding tissues through their power of amoeboid motion.[1,4] In this penetration they may be aided, in some instances, by the action of a spreading factor (hyaluronidase), formed by the tumor, softening and weakening the resistance to invasion of surrounding connective tissue.[5]

Summary

The adhesiveness of human glandular carcinoma cells, as compared to normal cells, was estimated by shaking cancerous and corresponding normal tissues in a mechanical agitator. The number of cells dislodged and separated was counted, and photographs of shaken and unshaken tissues were compared for cellularity and relative numbers of cells removed.

In twenty of twenty-one experiments, more cells were shaken out of cancerous than out of normal tissue, as revealed by photographs; and counts of separate cancer cells were correspondingly higher than were those of normal cells.

This result is in agreement with previous studies on squamous-cell cancers by another method, and justifies the conclusion that the mutual adhesiveness of human carcinoma cells is less than that of corresponding normal cells. The conclusion is consistent with the hypothesis that the invasive character of cancers is in part the result of decreased cellular adhesiveness.

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THE ASSOCIATION OF BREAST AND PELVIC DISEASE

VIRGINIA K. PIERCE, M.D. and DANELY P. SLAUGHTER, M.D.

BECAUSE of the obvious functional relationship between the female pelvic organs and the mammary glands, this study was instituted to determine whether women with breast cancer showed a higher incidence of pelvic disorders than do those who are normal. To that end, the gynecological status was determined in 100 unselected patients referred because of breast lesions: sixty-three women with breast cancer in various stages and thirty-seven with benign breast lesions.

Detailed gynecological and obstetrical histories were taken and where prior pelvic surgery had been done, operative reports and microscopic sections were obtained. All pelvic examinations were made by the same gynecologist in order that there might be a minimal variation in clinical evaluation. All abnormalities requiring treatment were referred to the Gynecological Service for adequate care. Routine Papanicolaou smears and, when possible, endometrial biopsies were made at the first examination; and all lesions requiring microscopic definition were subjected to biopsy. The endometrial biopsies were obtained by the Novak curette, four samples being taken, one from each lateral wall from the cornu downward and one each from the anterior and posterior uterine walls. The scrapings also included material from the endocervix. Endometrial biopsies could not be obtained in very aged patients owing to the senile atrophy and cervical stenosis. Moderately forceful attempts were made to open these stenoses with a small probe, a precautionary measure against the possibility of corpus carcinoma productive of concealed bleeding developing at some later date. This procedure is particularly important in those patients who are to be treated with stilbestrol for carcinoma of the breast. One of our early patients who received stilbestrol, a woman 72 years of age with a cervical stenosis that could not have been opened without considerable trauma, later developed an extensive hematometra while on the estrogen therapy.

Vaginal smears were taken at each initial examination and at all subsequent routine follow-up visits. Those who had no pelvic lesion at the first visit were re-examined routinely every three months, when endometrial biopsies and smears were taken. Patients treated with estrogens or androgens for breast carcinoma had pelvic examinations at intervals of one or two weeks; and endometrial biopsies and vaginal smears were repeated at each visit. Sufficient tissue could not be obtained for hematoxylin-eosin sections in those postmenopausal patients with endometrial atrophy but vaginal smears were of value.

In considering gynecological lesions in the patient's past history, only those requiring excisional pelvic surgery or radium therapy were tabulated. Patients with histories merely of retroversions, sterility, irregular menses, etc., were not included. In determining the percentage of patients having pelvic lesions at the first examination, inflammatory conditions such as salpingitis or trichomonas vaginitis were not included, nor were perineal or cervical lacerations, retroversions, cystocele, or rectocele.

Even after these exclusions, a high incidence of demonstrable lesions of the reproductive organs in women with breast conditions remained. Table 1 gives the over-all figures.

TABLE 1

DISEASE OF THE REPRODUCTIVE ORGANS IN PATIENTS WITH BREAST LESIONS

Those with previous gynecological surgery	26.0%
Those having gynecological lesions on first examination	48.0%
Those developing gynecological disease while being followed	9.0%
TOTAL	83.0%

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Table 2 lists the types of lesions found in those patients who had demonstrable positive pelvic findings at first examination. These are compared with the incidence of pelvic lesions in a group of presumably well women of comparable ages, using the figures published by Dr. Augusta Webster from the Cancer Detection Clinic of the Women's and Children's Hospital of Chicago. Examination of 2000 patients at that clinic showed an incidence of 23.6 per cent demonstrable pelvic lesions.

Squamous-cell carcinoma of cervix	5	11 cases or 55%
Adenoacanthoma of cervix	1	
Adenocarcinoma of corpus	4	
Carcinoma of vulva	1	
Carcinoma of thyroid	2	
Carcinoma of rectum	1	
Carcinoma of head and neck	4	

This again illustrates the association of breast and genital disease (in 55 per cent). Other studies of the association of breast cancer and cancer of the female reproductive organs bear this out. In a statistical review of patients with double primary cancers, Slaughter found that of 128 patients with

TABLE 2

TYPES OF LESION FOUND AT FIRST EXAMINATION

	Authors' Series	*Webster's 2000 Patients*
Cervical erosion	16.0%	13.6%
Kraurosis vulvae	8.0%	0.1%
Fibroids	19.0%	5.3%
Cervical polyps	13.0%	3.0%
Bartholin cyst	1.0%	0.5%
Procidentia	1.0%	1.3%
Carcinoma of cervix (In patients with breast cancer)	1.0%	
Carcinoma of corpus (In patients with breast cancer)	1.0%	
Carcinoma of ovary (In patients with breast cancer)	1.0%	
Patients showing postmenopausal estrogen activity	33.0%	

It is interesting to note that the incidence of fibroids was almost four times as great in those with breast disease as in the general female population; of kraurosis vulvae, eighty times; and of cervical polyps, four times.

Unsuspected double primary cancers were found on routine pelvic examination in three of our 100 patients: two of the uterus and one of the ovary. None had symptoms referable to the second cancer at the time it was first discovered. The second primary in the uterus (one in the cervix and one in the corpus) would have been missed on clinical examination alone, i.e., these lesions were diagnosable only by routine endometrial and cervical biopsies. The ovarian carcinoma was diagnosed at laparotomy, the patient having been referred to the Gynecological Surgery Service because of an ovarian mass the size of a lemon.

Our incidence of double primary cancers (breast and pelvis) in 3 per cent of the cases is higher than that reported by Taylor (1.2 per cent). His eighteen cases of malignant tumors developing in coincidence with breast cancer at Memorial Hospital included:

cancer of the breast and another primary malignant tumor, the second primary tumor involved the genitalia in 46 per cent. Although the total incidence of associated breast and other primary cancers is small, the second lesion is most often pelvic when such association does occur. Speert, in an as yet unpublished paper, has also noted the common association between mammary tumors and uterine cancer, particularly cancer of the corpus.

A comparison between the association of benign and of malignant breast lesions with positive pelvic findings shows that patients with benign breast lesions had a considerably higher incidence of gynecological aberrations.

Thus the incidence of previous gynecological disease and surgery was much higher in patients with benign breast lesions than in those with malignant, although an equal percentage was found to have pelvic lesions when first examined. In both, fibromyoma was the pelvic lesion most frequently requiring surgery. Fibroids were found in 18 per cent of the authors' patients on first examination, in comparison with 5.3 per cent

TABLE 3

ASSOCIATION OF BENIGN AND MALIGNANT BREAST LESIONS WITH PELVIC DISEASE

	Benign	*Malignant*
Number of breast patients	37	63
Patients with history of previous gynecological disease	50%	19%
Patients with previous uterine lesions	37%	14%
Patients with previous uterine surgery	33%	14%
Patients with fibroids in the past	25%	12%
Patients with previous ovarian surgery	12%	4.7%
Patients with pelvic disorders on first examination	48.6%	47.6%

found by Webster in the general female population.

The incidence of associated pelvic disorders at first examination in the 100 breast cases was 48 per cent, or twice that reported by Webster in the general population. This high incidence has impressed us with the importance of pelvic examinations in all breast cases even though the patient may deny any symptoms. The 10 per cent of patients who developed pelvic disease during the two years that they were followed in the breast clinic makes it imperative that pelvic examinations be carried out at three- to six-months' intervals.

An interesting ancillary finding has been the change in pelvic organs of patients with breast cancer treated either by androgens or estrogens. This study is by no means complete but is mentioned here because of the relationship to the original study. We are continuing the endometrial and cervical biopsies and vaginal smears on patients receiving tremendous doses of estrogen and androgen in order to attempt to correlate the various endocrine responses. It was of interest to note that great variations occurred in response to the hormones given. Some patients showed amazing changes in uterine size, shape, and consistency, while other patients of the same age and on the same medication showed very little response. Our cases are too few in number to attempt to correlate the reaction of breast carcinoma to estrogens with the response in the pelvic organs. However, the gynecological studies may prove to be of value as an index of the patient's utilization of estrogen. Roughly one-third of the postmenopausal patients with breast carcinoma showed vaginal smears indicative of estrogen activity at first examination, although some of these patients were ten to fifteen years past the climacteric. All denied hormonal therapy by other physicians before the smear was taken. In most of these cases, the endometrium was either atrophic microscopically or too little tissue could be obtained for hematoxylin-eosin sections. This would seem to indicate that the vaginal mucosa may still show estrogen influence when the hormonal level is too low to be reflected in the endometrium. It was also noted that the vaginal mucosa responded to administered estrogens before cervical and uterine changes were apparent. In some patients, the estrogen response ceased with the vaginal change and even though the dose of stilbestrol was increased and the medication continued for long periods of time, further cervical and endometrial changes did not occur. In other patients of the same age and with the same medication, marked cervical and uterine changes were noted both in enlargement of the uterus and in endometrial growth. Several patients developed extensive endometrial hyperplasia. Eight elderly women with atrophic, clean cervices developed cystic cervicitis followed by an extensive squamous metaplasia. The patients who had had previous surgical or roentgen-ray castration showed the same estrogen response patterns as did those with intact or untreated ovaries. Again, these cases are too few in number to warrant any conclusions concerning these extremely variable responses.

SUMMARY AND CONCLUSIONS

One hundred women with breast disease were subjected to a gynecological survey, including detailed histories, endometrial biopsies, and vaginal smears. Eighty-three were found to have had or to have demonstrable pelvic disorders of significant type, either in

the past, at the first examination, or which developed while they were under observation. This did not include inflammatory lesions and changes resulting from obstetrical wear and tear. The patients with benign breast lesions had more than twice as many pathological changes in the female reproductive organs as had those patients with breast cancer. The incidence of pelvic disease in the entire group was nearly four times that of well women of comparable age.

These results show the association of a cancer tendency in the two systems, so that some common etiological factor might well be indicted. Clinically they point, unassailably, to the duty of the general surgeon to include a pelvic examination in the investigation of every woman with a breast lesion.

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STUDIES OF LIVER FUNCTION IN PATIENTS HAVING CANCER OF THE BREAST

H. J. TAGNON, M.D.* and J. B. TRUNNELL, M.D.

SINCE the discovery by Lacassagne of the effectiveness of administered estrogens in the production and growth of mouse mammary cancer, the question has arisen whether estrogens play a role in the genesis of cancer of the human breast. It is at least conceivable that overstimulation of the glandular tissue of the breast by excessive quantities of estrogens might lead to the formation of human mammary cancer. A similar stimulus has been postulated by some authors as an etiological factor in certain uterine cancers in the human.[1,5] These authors believe that overstimulation of the uterine mucosa in certain instances of uterine cancer is the result of the presence of excessive quantities of estrogens, and that this may sometimes be ascribed to failure of the livers of these patients to inactivate estrogens.[2] It is well known that the liver is the organ concerned in estrogen inactivation in many animal species.[8] Observations suggesting that the same process exists in the human have thus far been limited,[10] but there is at least no experimental evidence to the contrary.

In view of these facts and postulates, a study of liver function in patients with cancer of the breast appeared justified. The results of such study are presented in this report.

MATERIAL AND METHODS

Three groups of women were investigated.

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We are indebted to Dr. Frank E. Adair for permission to study his patients (Group I); to the Breast Research Clinic for referring Group-II patients; and to the cancer prevention clinics of various hospitals, particularly the Kate DePew Strang Cancer Prevention Clinic of Memorial Hospital and Dr. Emerson Day of the Kip's Bay Cancer Prevention Clinic for referring patients in Group III.

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The first consisted of twenty-seven patients admitted on the wards of Memorial Hospital for radical mastectomy. Studies were conducted in the preoperative period. These patients were considered operable and had no clinical or roentgenographic evidence of metastases beyond the level of the axillary nodes.

Thirty-seven patients with inoperable or metastatic breast cancer were in the second group. The inoperability was attributable to metastases beyond the level of the axillary nodes. Some of these patients had undergone radical mastectomies in the past and were under treatment for local recurrences with or without metastases. This second group was studied prior to the institution of hormonal treatment in the breast clinic of this hospital.

The third comprised twenty-seven normal women of approximately the same age and social environment as the patients of the other two groups. They were referred to us by the cancer prevention clinic of this and other hospitals, after having been examined and declared free from cancer and from any other detectable disease.

Diagnoses were made by history and physical examination, roentgenographic studies, and laboratory procedures. In the first two groups, diagnoses of the primary lesion were always confirmed by pathological examination of sections or aspiration biopsies. Metastases in the second group of patients were shown clinically, roentgenographically, and by laboratory studies, and in certain instances by pathological study of available specimens. Complete autopsy reports were not available in any patient.

Selection of Patients. In the first two groups the patients were unselected; they were studied as they came to the hospital. The control patients (Group III) were selected on the basis of age, to constitute a group comparable in this respect to the two others.

Age. In group I the average age was 49.7 years with a range of 22 to 65 years. In group II, the average was 50.7 years, the range 27 to 80. In group III, the average age was 47.0 years; the range extended from 36 to 67 years.

Nutritional status was appraised by the history and general appearance, the weight, and the detection of clinical signs of nutritional deficiencies: it was good in all patients in group I; but unsatisfactory in cases 6, 7, 14, 25, 27, 36, and 38 of group II.

Status of the Liver. Clinical evaluation of liver damage was estimated by questioning the subjects about the existence of past liver disease, exposure to alcohol and other toxic agents, and the detection of signs of liver disease by physical examination.

In group I, only one patient presented clinical evidence of liver disease: her liver was definitely enlarged on palpation. Several patients in group II showed clinical evidence of liver disease (see Table 2). Group III showed no clinical evidence of liver disease.

Liver-Function Tests. No patient was febrile when the tests were carried out. The following liver-function tests were made on each subject:

1. Serum-Bilirubin Determination. This was done by the method of Malloy and Evelyn as modified by Ducci and Watson. The total and one-minute prompt-direct values were reported.

2. Bromsulfalein-Excretion Test. This was done by the method of Mateer et al., using 5 mg. of the dye per Kg. and a 45-minute period. Estimation of the dye in serum was done by the comparator block method and colorimetrically according to the method of Gaebler. The values obtained by the two methods never differed by more than 2 per cent.

3. Hippuric-Acid Synthesis. This was studied by measuring the amount of hippuric acid excreted in the urine in one hour after the intravenous injection of 1.77 gm. or sodium benzoate in 20 ml. of water. One ml. of phenolsulfonphthalein solution was injected intravenously immediately following the sodium benzoate and the amount of dye excreted measured in the urine after one hour. The results of the hippuric-acid test were not considered significant when the phenolsulfonphthalein excretion was below 35 per cent.

4. Thymol-Turbidity and Cephalin-Flocculation Tests. These were done as described elsewhere.[9] The thymol-turbidity test was carried out at *p*H 7.8 in the first two groups of patients, as recommended in the original procedure. This was modified to *p*H 7.5 according to the recommendation of Mateer et al., and the test carried out at this *p*H in the last group of subjects. The test, as carried out in groups I and II, may therefore not be strictly comparable to the test used in patients of group III.

Normal Values. For purposes of comparison, the following normal values were adopted for each test:

Bromsulfalein-Excretion Test. A maximum of 5 per cent retention after forty-five minutes.

Cephalin-Flocculation Test. The higher limit of normal was considered to be a 1 + reaction in twenty-four hours.

Thymol-Turbidity Test. A turbidity corresponding to 1.7 ml. of standard barium-sulfate suspension was considered the highest limit of normal.[9]

Serum-Bilirubin Test. The highest normal limit was taken to be 1.0 mg. for the total bilirubin and 0.4 mg. for the one-minute (prompt-direct) value.

Hippuric-Acid Test. A minimum excretion of 0.95 gm. of hippuric acid.

These conventional values for normal as used here are probably too liberal, but the meaning of normal values as described in the literature is very restricted when one deals with subjects of a different age group than those on whom the published normal values were obtained. In this study the purpose was not a comparison of the values obtained on the patients with normal standards but with a group of alleged normal subjects of the same age group and from the same social and economic environment.

The clinical and pertinent laboratory data are shown in Tables 1, 2, and 3. The phenolsulfonphthalein excretion is given only for

those patients who had an abnormal hippuric-acid test.

Results of Liver-Function Tests

Group I (*see Table 1*). Seven patients had an abnormal retention of bromsulfalein in the blood, and ten had an abnormal hippuric-acid test. In one the test could not be evaluated because of the poor kidney function revealed by a phenolsulfonphthalein excretion below 35 per cent (case 21).

The thymol-turbidity test was abnormal in three patients, and the cephalin-flocculation in three also. The total bilirubin level was elevated in five patients and the prompt-direct bilirubin, in seventeen patients. If the prompt-direct bilirubin values are disregarded, there is no consistent correlation among the abnormal tests, since only six patients in this group had more than one abnormal test (cases 5, 8, 10, 12, 18 and 25), and but two patients more than two positive tests (cases 8, 10). In one patient only were all the tests except the cephalin-flocculation distinctly abnormal (case 12).

Group II (*see Table 2*). Twenty-two of the thirty-seven patients in this group had an abnormal bromsulfalein clearance. The excretion of hippuric acid was abnormal in five of twenty-four patients on whom significant results were obtained. In four patients the test could not be evaluated because of impaired kidney function as shown by the low phenolsulphthalein excretion (cases 2, 8, 16, 32). The thymol-turbidity test was abnormal in fourteen patients, and the cephalin-flocculation in six. The total serum bilirubin was elevated in six and the prompt-direct in twenty. Leaving out the prompt-direct bilirubin values, fifteen patients in this group had more than one abnormal test, and five more than two. Abnormalities in all five tests were not observed in this group. A clinical diagnosis of liver metastases was made in six (cases 2, 12, 13, 15, 18, and 33).

Group III (*see Table 3*). An abnormal bromsulfalein clearance was noted in three patients. A low level of hippuric-acid excretion was observed in four of nineteen patients in whom significant results were obtained. The thymol-turbidity test was abnormal in ten, and the cephalin-flocculation in eight. An elevated serum total bilirubin existed in three patients and an elevated prompt-direct value in nine. Six subjects had more than one positive test, and two had more than two.

Discussion

The data show that the incidence of abnormal liver-function tests in the patients of group I was rather high. Especially striking was the high incidence of an abnormally low level of excretion of hippuric acid among these patients. However, the number of patients showing more than one abnormal test is small (six). Considering that one isolated abnormal test probably cannot be considered as irrefutable evidence of liver damage, one would conclude that six patients in this group had definite liver dysfunction as shown by the tests used in this work. In the others, liver dysfunction was either slight or absent.

The values for the prompt-direct serum bilirubin will not be considered in the following discussion. They have been included in the tables because interest in this fraction of the serum bilirubin has been aroused in recent years by its behavior in cases of infectious jaundice. Despite the studies of Watson et al. on the prompt-direct bilirubin, the significance of its elevation with or without elevation of the total serum bilirubin is still obscure.[3]

When the results of the tests in patients of group I are compared with those of group III, it appears that the number of patients with one positive test in group III is comparable to that found in group I. This is in part attributable to the higher incidence of positive thymol-turbidity tests in group III than in any other group. This high incidence of positive thymol-turbidity tests in group III may be due to the different technique of carrying out the test in this group. Excluding the thymol-turbidity test from consideration, if the other tests are compared in groups I and III, it appears that the incidence of positive tests is still approximately the same in the two groups and the number of patients with more than one positive test approximately the same in both groups. The most remarkable difference between the two groups con-

sists in the higher incidence of abnormal values for the bromsulfalein and hippuric-acid tests in group I and the higher incidence of positive cephalin-flocculation tests in group III. The significance of this difference is not apparent at the present time.

On the whole, the patients of group II exhibited a higher incidence of abnormal tests than those of the two other groups. This was true especially for the bromsulfalein test which was found to be abnormal in almost two-thirds of these patients as compared to one-fourth of the patients in groups I and III respectively. The proportion of elevated thymol-turbidity values was also higher than in the other two groups. The incidence of abnormal hippuric-acid tests was low. This fact is interesting because the patients of group II were in the more advanced stages of breast cancer. One would therefore expect the incidence of abnormal hippuric-acid tests to be at least as high in group III as in group I, were there a correlation between the result of the test and the presence of cancer of the breast. The relatively low incidence of defective hippuric-acid synthesis in patients of group II would seem to render insignificant the high incidence of the defect in patients of group I.

Conclusion

The incidence of abnormal liver-function tests was found rather high in a group of twenty-seven patients with operable cancer of the breast. However, this was not strikingly different from that found in a control group of twenty-seven presumably normal subjects of the same age group and belonging to the same social and economic level. The proportion of abnormal tests was higher in a group of thirty-seven patients with inoperable, metastatic cancer of the breast. This could not be attributed to liver metastases in all instances. There are many factors in patients with extensive carcinoma and metastases that might conceivably alter liver function, among which apparent or hidden malnutrition associated with poor appetite, and anemia are probably the most important. It appears probable that the liver dysfunction in this group of cases of inoperable cancer was caused by these factors and perhaps others depending directly or indirectly on the presence of cancer.

Summary

1. The liver was studied in three groups of subjects by bromsulfalein excretion, hippuric-acid synthesis, thymol-turbidity, cephalin-flocculation, and serum-bilirubin tests. The three groups were: group I comprising twenty-seven patients with operable cancer of the breast; group II, thirty-seven patients with inoperable cancer of the breast, the inoperability being due to extensive metastases; group III, consisting of presumably normal subjects in the same age group and from the same social and economic environment as the other two.

2. Although there was a rather high incidence of abnormal tests in the first group of patients, this was not significantly different from that found in the third group. The bromsulfalein excretion and hippuric-acid synthesis were the tests most often found abnormal in patients with operable cancer of the breast (group I).

TABLE I

LIVER-FUNCTION TESTS IN PATIENTS WITH OPERABLE CARCINOMA OF THE BREAST

Number Initials Age	Gravida	Pathology	Metastases	Bromsulfalein % in 45 min.	Hippuric-acid gm.†	Thymol turbidity ml	Cephalin-flocculation in 24 hrs.	Bilirubin	
								Total	Prompt-direct mg. %
1 L.G. 65	7	Colloid ca. gr. II	0	0	0.69(40)	0.25	0	0.44	0.06
2 G.W. 49	0	Infiltr. duct ca., gr. II	Axillary nodes	2	1.07	1.25	2+	0.39	0.28
3 A.D. 47	1	Infiltr. duct ca., gr. II	Axillary nodes	4	—	0.50	0	0.84	0.15
4 E.S. 49	2	Infiltr. duct ca., gr. II	Axillary nodes	0	1.2	1.15	0	*1.24*	0.34
5 R.V. 57	2	Medullary & infiltr. duct ca., gr. III	Axillary nodes	*8**	1.04	1.70	0	*1.35*	*1.24*
6 G.G. 33	1	Infiltr. mammary ca.	0	0	0.98	1.45	0	0.39	0.33
7 A.G. 56	0	Infiltr. duct ca., gr. III	Axillary nodes	2	*0.75*(40)	0.95	0	0.79	*0.68*
8 M.M. 45	0	Infiltr. duct ca., gr. III	Axillary nodes	*16*	*0.72*(35)	0.70	*1–2+*	0.22	0.16
9 H.B. 60	0	Infiltr. duct ca., gr. III	Axillary nodes	2	*0.74*(35)	0.35	0	0.22	0.16
10 R.P. 52	2	Mammary ca.	Axillary nodes	*8*	1.31	0.15	2+	0.79	*0.73*
11 E.B. 56	1	Infiltr. duct ca., gr. II	0	2	1.37	0.95	0	0.84	*0.73*
12 L.F. 50	0	Comedo and infiltr. duct ca., gr. II	Axillary nodes	*32*	*0.92*(60)	*5.35*	1+	*1.35*	*1.18*
13 M.P. 54	3	Comedo ca.	Axillary nodes	2	1.39	0.90	0	0.56	0.39
14 A.C. 42	1	Infiltr. duct ca., gr. III	Axillary nodes	2	1.50	1.15	0	0.56	*0.50*

TABLE 1 (*Continued*)

Number Initials Age	*Gravida*	*Pathology*	*Metastases*	*Bromsulfalein % in 45 min.*	*Hippuric-acid gm.†*	*Thymol turbidity ml*	*Cephalin-flocculation in 24 hrs.*	*Bilirubin*	
								Total	*Prompt-direct*
								mg. %	
15 G.L. 50	0	Infiltr. ca. gr. III	0	2	*0.93*(40)	0.90	0	0.73	*0.67*
16 N.S. 61	7	Infiltr. duct ca., gr. III metaplasia	Axillary nodes	4	*0.93*(40)	1.20	0	0.22	0.16
17 M.D. 57	6	Lobular & infiltr. duct. ca., gr. III	Axillary nodes	4	1.25	1.00	0	0.90	*0.84*
18 M.S. 57	0	Infiltr. duct. ca., gr. II	Axillary nodes	4	*0.71*(45)	1.15	0	*1.12*	*1.01*
19 E.L. 39	4	Medullary ca.	0	0	1.48	1.70	0	0.84	*0.78*
20 C.K. 62	2	Comedo and infiltr. duct ca., gr. II	0	4	*0.56*(35)	0.90	0	0.51	*0.45*
21 V.I. 54	2	Medullary ca.	0	2	0.15(10)	1.30	0	0.73	*0.67*
22 P.P. 55	0	Comedo and infiltr. duct ca., gr. III	Axillary nodes	0	*0.79*(60)	0.95	0	0.28	0.22
23 M.D. 38	1	Medullary ca.	Axillary nodes	4	1.54	*2.40*	—	0.56	*0.45*
24 S.B. 63	3	Infiltr. duct. ca., gr. II	0	*14*	1.39	1.70	—	0.84	*0.84*
25 V.D. 32	0	Infiltr. duct ca., gr. III	Axillary nodes	*6*	—	0.65	0	*1.01*	*0.79*
26 M.F. 37	1	Infiltr. duct ca., gr. III	Axillary nodes	*24*	—	1.25	0	0.51	*0.51*
27 F.P. 22	0	Infiltr. duct ca., gr. III	Axillary nodes	2	1.47	*2.15*	0	0.73	*0.62*

* Figures in italics are abnormal values. † Values of PSP excretion are indicated in parentheses.

TABLE 2

LIVER-FUNCTION TESTS IN PATIENTS WITH INOPERABLE CARCINOMA OF THE BREAST

Number Initials Age	*Gravida*	*Pathology*	*Metastases*	*Clinical evidence of liver disease*	*Bromsulfalein % in 45 min.*	*Hippuric-acid gm.*	*Thymol-turbidity ml.*	*Cephalin-flocculation (24 hrs.)*	*Bilirubin*	
									Total	*Prompt-direct*
									mg. %	
1 R.T. 80	0	Infiltr. duct ca., gr. III, bilat.	0	Liver enlarged 2 cm.	*20*	1.05	1.0	0	0.73	*0.56*
2 R.T. 46	2	Mammary ca.	Mult.	Jaundice, ascites	—	0.15(15)	*1.9*	*3+*	*3.82*	*2.86*
3 A.R. 32	1	Mammary ca.	Mult. bone metas.	—	*8*	1.19	1.60	0	0.16	0.10
4 C.M. 63	—	Mammary ca.	Local recurr.	—	2	1.26	1.20	1+	0.73	*0.62*
5 A.S. 47	2	Medullary and comedo ca., gr. III	Lung	0	*12*	—	1.10	0	0.51	*0.45*
6 Y.L. 27	0	Infiltr. duct ca., gr. III	Liver, lung	Liver enlarged 5 cm.	*22*	1.71	*2.75*	0	0.28	0.22
7 F.W. 43	1	Medullary ca. grade II	Neck, pleura	—	*6*	1.25	*2.40*	0	—	—
8 N.T. 59	2	Mammary ca.	Skin of neck, lungs, brain	—	*6*	0.23(15)	0.75	0	0.7	*0.67*
9 E.N. 82	—	Mammary ca.	Axilla, neck	—	5	*0.91*(60)	*3.65*	*4+*	0.84	*0.78*
10 F.W. 47	0	Mammary ca.	Lung, pleura	Liver enlarged	2	*0.78*(35)	*2.55*	*4+*	0.17	—
11 M.O. 51	4	Mammary ca.	Axilla, second breast	0	*20*	1.06	1.10	0	*1.69*	*1.63*
12 R.L. 46	*0*	Infiltr. duct ca., gr. III	Recurrent and metastatic to skin and gastro-intestinal tract	Multiple abdominal metastases	*0*	1.28	1.00	0	*0.45*	0.31
13 M.F. 27	0	Comedo duct ca. breast, gr. II	Lymph nodes	Liver enlarged 3 cm.	5	1.15	1.57	0	0.33	0.22

TABLE 2 (*Continued*)

Number Initials Age	*Gravida*	*Pathology*	*Metastases*	*Clinical evidence of liver disease*	*Bromsulfalein % in 45 min.*	*Hippuric-acid gm.*	*Thymol-turbidity ml.*	*Cephalin-flocculation (24 hrs.)*	*Bilirubin*	
									Total	*Prompt-direct*
									mg. %	
14 K.A. 42	—	Infiltr. duct ca., gr. III	Nodes, bones	Liver enlarged 13 cm.	23	1.17	2.23	4+	0.28	0.17
15 E.B. 53	2	Mammary ca.	Pleura, right lung	Liver enlarged 6 cm.	8	—	1.35	0	0.73	0.56
16 V.T. 39	—	Infiltr. duct ca., gr. III	Spine, pelvis	0	2	0.89(25)	4.15	0	0.67	0.56
17 H.A. 54	—	Infiltr. duct ca. Gr. III	Neck nodes, mandible, widespread skeletal	0	5	1.62	2.20	0	0.28	0.17
18 A.C. 58	2	Infiltr. duct ca., gr. III	Widespread skeletal	Obstructive jaundice	49	—	4.05	0	22.93	17.42
19 C.B. 52	0	Infiltr. duct ca., gr. III	Calvarium, spine, ribs	—	12	—	2.65	3+	0.56	0.50
20 J.M. 60	0	Infiltr. duct ca., "sweat-gland type"	Lung, in situ	0	—	—	—	0	—	—
21 E.A. 47	0	Mammary ca.	Spine, pelvis	0	24	1.12	1.15	1-2+	0.89	0.83
22 L.W. 39	0	Mammary ca.	Skin	0	5	1.11	1.00	0	0.61	0.55
23 B.S. 71	6	Epidermoid ca., gr. II	Supra-clavicular nodes	0	12	—	1.20	0	0.67	0.61
24 S.D. 45	4	Mammary ca.	Lung, multiple	0	2	1.40	2.65	0	0.56	0.45
25 G.Q. 64	0	Mammary ca.	Skin, spine, pelvis, lung	Liver enlarged	24	0.74(50)	1.30	0	—	—
26 I.D. 49	1	Mammary ca. recurrent	Skin, nodes, lung	0	8	—	0.70	0	0.28	0.22

TABLE 2 (*Continued*)

Number Initials Age	*Gravida*	*Pathology*	*Metastases*	*Clinical evidence of liver disease*	*Bromsulfalein % in 45 min.*	*Hippuric-acid gm.*	*Thymol-turbidity ml.*	*Cephalin-flocculation (24 hrs.)*	*Bilirubin*	
									Total	*Prompt-direct*
									mg. %	
27 A.W. 52	4	Infiltr. duct ca., gr. III	In situ	0	2	1.77	1.40	0	0.39	0.28
28 B.J. 37	0	Infiltr. duct ca., gr. II	Skin, nodes, second breast	0	*17*	1.39	0.65	0	0.75	*0.64*
29 M.B. 36	1	Mammary ca.	All bones	0	3	*1.55*	1.65	0	0.56	*0.50*
30 K.G. 60	0	Mammary ca.	Lung	0	*32*	0.99	1.20	0	0.33	0.27
31 M.K. 44	0	Infiltr. duct ca., gr. III	Lung	0	*12*	—	0.90	0	0.22	0.16
32 R.D. 54	4	Mammary ca.	All bones	0	2	0.86(30)	0.10	0	*1.52*	*1.46*
33 A.C. 59	2	Infiltr. duct ca., gr. III	Bones, presum. liver	Jaundice, clay-colored stools, liver enlarged	*49*	—	*4.05*	0	*2.58*	*1.17*
34 M.D. 55	1	Mammary ca.	Axilla	0	*6*	*0.46*(35)	*9.50*	1+	0.16	0.10
35 A.K. 73	7	Mammary ca.	Axilla	None, but heart failure present	4	*0.77*(35)	0.70	0	0.17	0.11
36 T.C. 39	0	Infiltr. duct ca., gr. III	Recurrent ca. and metas. to bones	0	*10*	1.67	*2.10*	1+	—	—
37 S.K. 45	0	Infiltr. duct ca., gr. II	Bones	0	*6*	1.29	1.80	1+	*1.07*	*0.90*

TABLE 3

LIVER-FUNCTION TESTS IN SUBJECTS FREE OF CARCINOMA

Number *Initials* *Age*	*Gravida*	*Bromsulfalein* *% in 45 min.*	*Hippuric-acid †* *gm.*	*Thymol-Turbidity* *ml.*	*Cephalin-Flocculation* *24 hrs.*	*Bilirubin* *Total* *mg. %*	*Bilirubin* *Prompt Direct* *mg. %*
1 R.B. 50	0	0	0.93(40)	0.95	0	0.22	0.16
2 L.B. 36	3	2	1.02	4.05	4+	0.17	0.11
3 J.C. 45	0	2	0.76(30)	2.20	3+	0.22	0.16
4 H.C. 52	0	4	1.17	1.45	0	0.22	0.16
5 F.E. 37	0	0	1.09	0.90	0	0.22	0.18
6 R.E. 54	2	2	0.82(25)	1.65	0	0.22	0.14
7 B.G. 48	2	2	0.79(15)	1.70	0	0.39	0.33
8 R.K. 53	5	4	0.95(25)	3.30	4+	0.17	0.11
9 L.K. 62	1	12	1.43	2.65	0	0.17	0.11
10 L.K. 59	2	0	0.71(40)	0.30	0	0.17	0.11
11 M.L. 47	0	0	1.09	2.40	0	0.39	0.28
12 M.M. 54	2	5	1.05	3.35	0	0.17	0.12
13 E.P. 60	2	2	1.28	0.63	0	0.17	0.11
14 H.P. 40	5	2	0.94(40)	0.83	0	0.28	0.23
15 E.R. 43	2	0	0.96	1.75	0	0.16	0.11
16 R.S. 54	4	0	0.42(20)	2.87	0	0.17	0.10
17 I.S. 62	5	2	0.81(20)	2.25	0	0.67	0.56
18 E.S. 56	2	2	1.64	1.15	0	1.13	1.01
19 R.W. 53	0	2	0.67(20)	2.0	3+	0.28	0.14
20 E.S. 58	0	2	0.80(40)	1.75	3+	0.79	0.73
21 L.W. 45	0	0	1.25	1.80	0	0.62	0.56
22 M.B. 49	0	8	0.96	0.35	0	1.18	1.08

TABLE 3 *(Continued)*

Number Initials Age	*Gravida*	*Bromsulfalein % in 45 min.*	*Hippuric-acid † gm.*	*Thymol-Turbidity ml.*	*Cephalin-Flocculation 24 hrs.*	*Bilirubin*	
						Total	*Prompt Direct*
						mg. %	
23 N.Z.	0	0	1.54	0.55	*3+*	0.62	*0.45*
37							
24 M.P.	0	0	0.47(10)	1.25	*3+*	0.62	*0.53*
47							
25 F.M.	0	4	1.00	0.80	*4+*	0.79	*0.73*
67							
26 G.M.	0	0	1.03	1.65	0	*1.28*	*1.07*
46							
27 P.L.	0	*12*	—	1.40	0	0.34	0.28
57							

* Figures in italics are abnormal values.
† Values of PSP excretion are indicated in parentheses.

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THE INFLUENCE OF DIET ON THE ABILITY OF RAT-LIVER SLICES TO DESTROY THE CARCINOGEN N,N-DIMETHYL-*P*-AMINOAZOBENZENE*

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DIET is an important factor in the production of liver tumors in rats when they are fed the carcinogen, N,N-dimethyl-*p*-aminoazobenzene (DMB). Several nutritional factors have been shown to influence tumor production by this agent, i.e., riboflavin, [7, 9] biotin,[2, 15] protein,[7] and fat.[8, 11] However, whether the influence of the dietary constituents is to be attributed to alterations in the rate or pathway of metabolism of DMB, to a change in the sensitivity of or ability to resynthesize one or more components of hepatic cells, or to other factors remains to be determined.

Since our earlier report that liver slices destroy DMB[5] in vitro, the effect of diet on this capacity of liver tissue has been investigated.

METHODS

The rats used in these experiments were of the Wistar strain obtained from the Wistar Institute in 1945 and inbred since that time. The animals used for the nutritional experiments weighed between 100 to 150 gm. at the start. The diets used were of the brown-rice–carrot type, which have been studied previously by this group for their effect on tumor production by DMB.[4]

The ability of rat tissue to destroy DMB in vitro was determined in the following manner. The tissues were suspended in 1.9 ml. Ringer phosphate solution, *p*H 7.4, and 100 μgm. of DMB or other azo dyes added in 0.1 ml. of 95 per cent ethanol. The tissues were then incubated aerobically, generally in small Erlenmeyer flasks, at 37.5°C. for the stated time interval. The tissue was killed at this point by the addition of 0.2 ml. of 11 N KOH. The tissue and solutions were transferred to a glass homogenizer[13] with the aid of 3.0 ml. of water and 4.0 ml. of methyl alcohol. After homogenization the mixture was transferred to 75 ml. test tubes, 20 mm. by 20 cm., with the aid of 3.0 ml. of methanol; 2.0 ml. of 11 N KOH was added to the mixture. After ten minutes the mixture was extracted with 5.0, 3.0, and 2.0 ml. portions of reagent-grade benzene. The layers were separated by centrifugation. The benzene extracts were combined, the DMB was extracted with 5.0, 3.0, and 2.0 ml. portions of 7 N HCl and the acid extract made up to a volume suitable for colorimetric assay with 7 N HCl. The optical density of this solution was determined in a spectrophotometer at 518 mμ and the amount of DMB calculated; 90 to 95 per cent of added DMB was recovered by this extraction procedure. However, in the case of brain tissue, several additional extractions were necessary. N,N-diethyl-*p*-aminoazobenzene (DEB) recoveries were also good (90 to 95 per cent), but *p*-aminoazobenzene (AB) recoveries were much less satisfactory (65 to 75 per cent).

The riboflavin content of rat liver was determined by a modification of the fluorometric method of Hodson and Norris.[3]

RESULTS

The destruction of DMB by liver slices under the conditions of these experiments was found to be proportional to the amount of tissue used, up to 200 mg., and to the duration of the incubation, up to ninety min-

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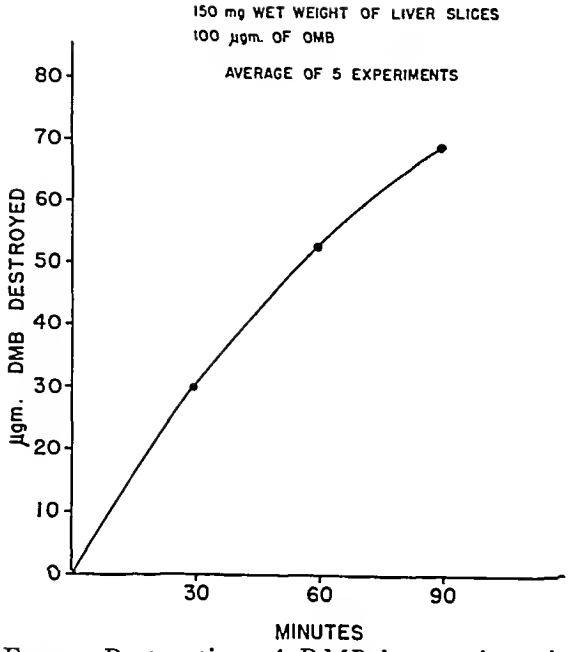

FIG. 1. *Destruction of DMB by rat tissue in vitro.*

utes. The rate of destruction of DMB as a function of time is not strictly linear, but falls off gradually. The average values for five experiments are plotted in Fig. 1. Liver slices of 150 mg. wet weight were used. The DMB is rapidly concentrated in the tissue slices: 50 to 85 per cent of the dye remaining at thirty minutes was found in the tissue. The cells observed microscopically appear to be diffusely stained yellow. The residual dye from several of the experiments in which normal-diet animals were used has been chromatographed[10] and no evidence of the accumulation of N-methyl-*p*-aminoazobenzene (MMB) or *p*-aminoazobenzene (AB) was obtained. No significant destruction of DMB has been observed using unfortified liver homogenates, in concentration up to 450 mg. per 2 ml., in place of liver slices.

The nature of the destruction of DMB has not been determined. As no highly colored compound, except DMB, has been detected in the destruction experiments, it is probable that the azo linkage is attacked. Ten experiments have been run with liver slices comparing destruction under aerobic, to destruction under anaerobic, conditions. The dye was destroyed under anaerobic conditions, but the amount varied from 50 to 100 per cent of that destroyed in the presence of oxygen.

Liver slices have also been found capable of destroying the related compounds, DEB and AB. The incubation of 100 µgm. of DMB, DEB, and AB with 150 mg. of liver slices for sixty minutes indicates that AB is destroyed more rapidly and DEB less rapidly than DMB. In four experiments in which liver slices from the same animal were incubated with 100 µgm. each of the dyes, 85 µgm. of AB, 54 µgm. of DMB, and 25 µgm. of DEB were destroyed.

The ability of rat tissues to destroy DMB in vitro under the conditions of these experiments is not limited to the liver. As is shown in Fig. 2, rat kidney-cortex slices destroy approximately one-half as much as liver, and spleen slices approximately one-fifth as much. Brain and testes minces and blood cells destroy very little under the same conditions. The numbers on the bars refer to the number of animals used. In this experiment and in the succeeding ones, 150 mg. (wet weight) of tissue was incubated for sixty minutes with 100 µgm. of the dye. No substrate such as glucose was added to the medium. However, four experiments with kidney and brain (not included in Fig. 2) have shown that the addition of glucose to the solution increased the average amount of DMB destroyed in sixty minutes—from 31 to 37 µgm. in the case of kidney, and from 4.3 to 5.0 µgm. in the case of brain. These results do not differ greatly from those presented in Fig. 2.

During the course of these experiments it was observed that liver slices from rats maintained on a high tumor-incidence diet (brown-rice–carrot–DMB) were able to destroy much less DMB than were the normal-diet (dog-chow) rats. An investigation of this lowered ability of the livers to destroy DMB in vitro has shown that this capacity of liver cells can be decreased by the high tumor-incidence diet (brown-rice–carrot) in the absence of the azo carcinogen. Data illustrating this point are shown in Fig. 3. The numbers in the bars refer to the number of animals used. It can be seen that the maintenance of rats on the brown-rice–carrot ration causes a decrease in DMB destruction by liver slices. The effect of maintenance on

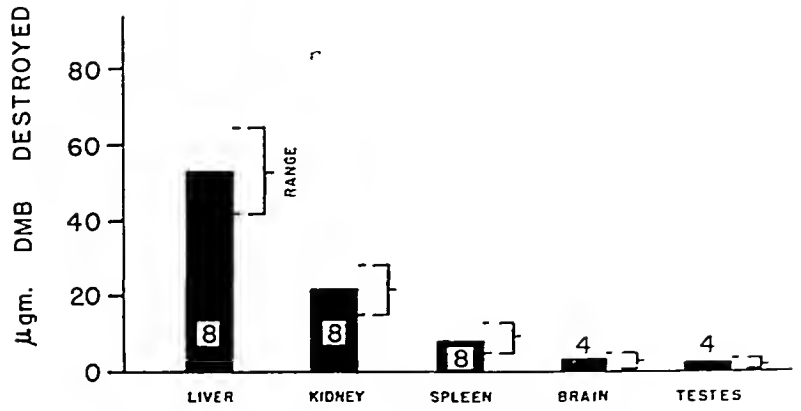

FIG. 2. *Destruction of DMB by liver slices.*

the rice diet appears to approach a steady value in eight to eleven days. Rats examined after thirty to forty days on the brown-rice diet fall in the same range as is shown in Table 1.

TABLE 1

DESTRUCTION OF DMB BY LIVER SLICES FROM RATS ON VARIOUS DIETS FOR 30 TO 40 DAYS

Diet	*No. rats*	DMB *Destroyed µgm.*	DMB *Range µgm.*
Normal	20	54	38-64
Brown rice	6	22	15-30
Brown rice + riboflavin + casein	6	47	40-54
Brown rice + riboflavin + casein + biotin	6	49	39-58
Brown rice + yeast	5	46	40-54

The difference between the livers of rats on a normal diet and those fed brown rice is apparent also in the destruction of *p*-aminoazobenzene (AB). In addition, since the solubility of AB is much greater than DMB in Ringer-phosphate solution (49 µgm./cc. as compared to 0.3 µgm./cc.), it was possible to measure this destruction in the presence and absence of ethanol which is used in the DMB experiments. The data, particularly in the case of the rice-diet animals, is less reliable than the DMB data because of the poor recovery (65 to 75 per cent) of added AB. As is shown in Table 2, the presence of alcohol in the solution depressed the ability of liver slices to destroy AB. However, the difference in the amount of AB destroyed by liver slices from normal-diet and rice-diet rats was striking both in the presence and absence of ethanol. Ethanol in the amounts used (0.1 cc.) inhibited the respiration of liver slices by an average of 28 per cent in six experiments.

The observation that the maintenance of

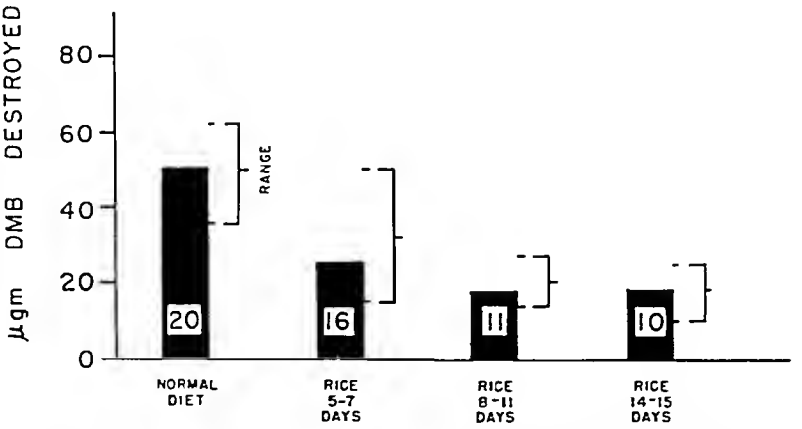

FIG. 3. *Relationship between the ability of rat-liver slices to destroy DMB and the period of maintenance on a brown-rice diet.*

rats on the high tumor-incidence diet lowered the capacity of liver slices to destroy DMB made it desirable to determine the effect of supplements that convert this basal diet into a protective diet. The addition of 15 per cent dried brewers yeast[12, 14] or riboflavin and 18 per cent casein[7] delays or prevents the production of liver tumors by DMB. As is shown in Fig. 4, these two protective diets enable the rat to maintain a normal ability to destroy DMB in vitro. The addition of casein alone, which is not protective,[7] did not. The addition of riboflavin alone, which is also not protective, gave intermediate values at the fourteen- to seventeen-day period.

Thus it appears that the capacity of rat-liver slices to destroy DMB in vitro gives an indication of the protective or nonprotective influence of different diets on the carcinogenic activity of DMB. Since biotin added to a riboflavin-rice-casein diet[15] as well as other types of protective diets[14, 15] has been observed to increase tumor incidence, biotin (20 μgm. per 10 gm. diet) has been added to the protective riboflavin-rice-casein diet. Insofar as this point has been studied, the evidence indicates that the addition of biotin to this diet is without effect on the ability of the liver cells to destroy DMB in vitro and hence its procarcinogenic activity would not be detected in this test. The data for the thirty- to forty-day period are shown in Table 2.

TABLE 2

DESTRUCTION OF *p*-AMINOAZOBENZENE (AB) BY 150 MG. LIVER SLICES IN 20 MINUTES

	AB			
	Destroyed μgm.	*Range* μgm.	*No. exp.*	*% inhibition by alcohol*
Normal-diet rats				
100 μgm. AB dissolved in Ringer-PO_4	49.8	37-60	5	
100 μgm. AB dissolved in 0.1 cc. alcohol	35.4	24-50	5	29
Brown-rice diet (14-20 days)				
100 μgm. AB dissolved in Ringer-PO_4	12.0	6-18	5	
100 μgm. AB dissolved in 0.1 cc. alcohol	10.5	6-18	5	13

It was reported by our group in 1940[6] that the riboflavin content of the livers of rats on the brown-rice–carrot ration was lower than normal rats and was even lower when DMB was included in the diet. The addition of protective supplements maintained normal or almost normal riboflavin levels in the livers. These results led to the discovery of the protection afforded by a riboflavin-casein supplement.[7] In view of the relationship between riboflavin level in the liver and tumor incidence, which has been emphasized by the

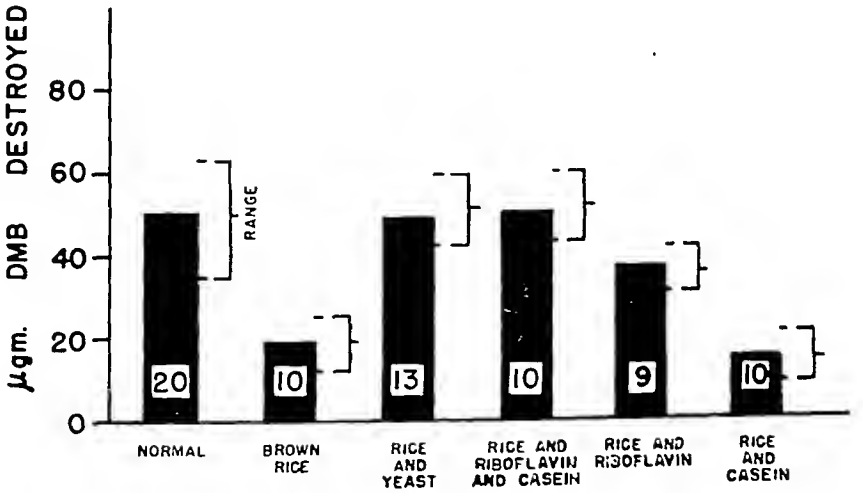

FIG. 4. *Destruction of DMB by liver slices from rats on various diets for fourteen to seventeen days.*

recent work of Griffin and Bauman,[1] and Miller,[9] a series of animals was studied in which both the riboflavin content and the ability to destroy DMB in vitro was measured. Twenty-nine rats fed a normal diet or a brown-rice diet, or rice plus casein, or rice plus riboflavin have been examined. The results are presented in Fig. 5. It can be seen that when the riboflavin content of the liver is low, the ability of the livers to destroy DMB in vitro is low. Thus, there appears to be a correlation between the riboflavin content of the liver and the ability of liver slices to destroy DMB in vitro in animals fed the brown-rice–type diet and no DMB.

Several experiments with normal-diet liver slices and brown-rice–diet liver slices have been tried, in which up to 50 μgm. of riboflavin has been added to the solution. The added riboflavin did not alter the amount of DMB destroyed in either case.

ity of liver cells to destroy the carcinogen DMB in vitro reported in this paper has been observed in the absence of DMB in the diet. Hence, this change represents a change in the function of liver cells, presumably either primarily or secondarily due to an alteration in a riboflavin-containing component, which is due to purely nutritional causes. It is not complicated by the toxicity of the carcinogen or its metabolites.

The observation that biotin, which has been shown to exert a procarcinogenic action in the production of tumors by DMB, was without detectable effect on the ability of liver slices to destroy DMB in these experiments was not unexpected. In the experiments on similar diets including DMB, in which the procarcinogenic activity of biotin was observed,[5] measurement of the riboflavin content of the tumor-bearing livers indicated that the riboflavin levels were in the normal

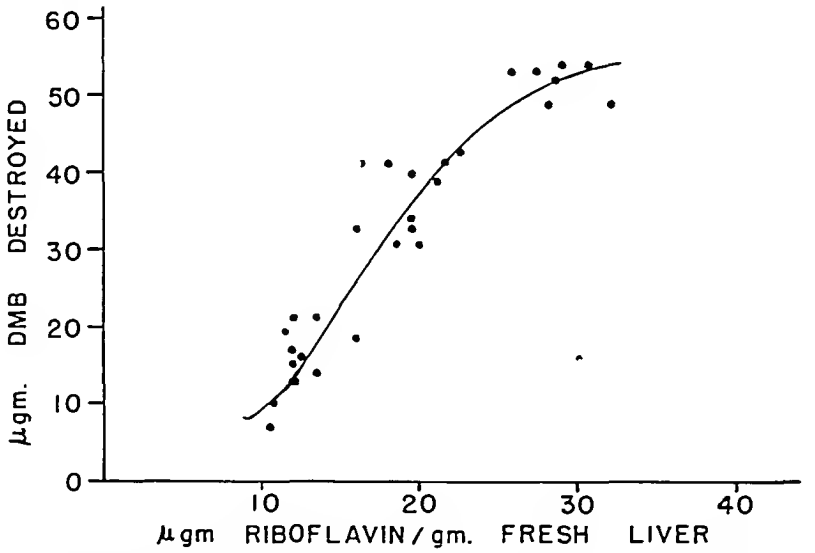

FIG. 5. *Relationship between the riboflavin content and the ability to destroy DMB in vitro.*

DISCUSSION

The observation that in vitro, liver is the most active tissue in destroying DMB lends support to the assumption that in vivo, the liver is the major site of metabolism of DMB. However, the relatively high activity of kidney-cortex slices suggests the possibility that at least a portion of the metabolites of DMB excreted in the urine may arise in this tissue.

The marked influence of diet on the ability of liver slices to destroy DMB in vitro appears to be related to the riboflavin content of the livers, the absence of biotin effect on the riboflavin content would, as a first assumption, suggest that biotin would fail to influence the ability of liver slices to destroy DMB.

The importance of the riboflavin content of the liver with respect to tumor incidence and its relation to the ability of livers to destroy DMB in vitro suggest that the protec-

tion usually associated with high riboflavin levels in the liver is related to the ability of hepatic cells to destroy the carcinogen. The procarcinogenic action of biotin in spite of a high level of riboflavin suggests the involvement of other mechanisms by which dietary factors may influence hepatic-tumor production by DMB in the rat. The experiments of Sugiura (quoted in[4]) indicating that diet can influence tumor incidence after DMB administration has been stopped, and hence when destruction of DMB is presumably no longer a factor, also indicates the involvement of other mechanisms by which diet can influence tumor production by DMB.

These studies are being extended to diets that do not contain brown rice and also to rats fed these diets containing the carcinogen DMB.

Summary

1. Liver slices, and to a lesser extent kidney and spleen slices, have been found to destroy the azo carcinogen, N,N-dimethyl-*p*-aminoazobenzene (DMB) in vitro. Brain and testes did not destroy significant amounts.

2. The ability of liver slices to destroy DMB is influenced by diet. Using diets of the brown-rice type, the high tumor-incidence, brown-rice diet was found to decrease the ability of liver slices to destroy DMB. The conversion of this diet to a protective diet by the addition of yeast or riboflavin and casein prevented this decrease. Biotin did not affect this function under the conditions studied.

3. As this effect of diet occurs without the inclusion of DMB in the diet, this change represents an alteration of hepatic-cell function produced by purely nutritional means.

4. Measurement of the riboflavin content of the livers and the ability of the liver slices to destroy DMB indicates that this function of hepatic cells is related to their riboflavin content.

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SOME EPIDEMIOLOGICAL FEATURES OF CANCER*

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IN studying any disease, we may think of those affected as a separate population, differing from the normal population not only in having the disease but in other respects as well. The term "epidemiology," applied to cancer, is used in this broad sense of indicating all knowledge regarding such differences. It may be defined further as the study of what persons or groups of persons are most likely to develop cancer and under what circumstances.

One of the most discussed aspects of the epidemiology of cancer has been the steady increase in cancer mortality that has occurred during the past century. This increase is usually attributed to two factors, the "aging" of our population and the improvement in diagnosis. The effect of the increasing proportion of older persons in the population can be ascertained readily by the statistical device of age-standardization, which consists in calculating what the mortality each year would have been had the proportion of people of various ages remained the same. Such data on cancer from 1850 on are available for England and Wales and, in this country, for the state of Massachusetts.

In England and Wales, the most rapid increase in (age-standardized) cancer mortality occurred, contrary to what we might expect, prior to 1895, that is, before the discovery of the roentgen rays. Since that time, mortality among females, when the effect of age is eliminated, has remained practically stationary. Among males, the increase continued after 1900, although less rapidly than before, and since 1920, the rate in males has exceeded that among females (Table 1 and Fig. 1).

In Massachusetts, the trend of mortality has been broadly similar to that in England, except that the changes in trend have occurred approximately twenty years later. The most rapid rate of increase was in the period from 1860 to 1915. After 1915, the rate in females levelled off and since 1935 has shown

TABLE 1
CANCER MORTALITY IN ENGLAND AND WALES,* 1851-1937
Standardized† Death Rates per 100,000 Population

Period	*Male*	*Female*
1851-55	20.0	42.8
1856-60	21.4	45.2
1861-65	24.3	50.4
1866-70	27.2	54.5
1871-75	31.0	59.4
1876-80	36.1	65.3
1881-85	41.8	70.1
1886-90	50.9	77.6
1891-95	58.5	85.0
1896-1900	68.8	91.1
1901-05	75.0	93.9
1906-10	81.4	94.4
1911-15	89.2	97.1
1916-20	90.2	94.8
1921-25	98.1	97.8
1926-30	‡	‡
1931-35	104.5	96.9
1936	106.8	96 9
1937	107.1	95.1

* Source: Registrar-General's Statistical Review of England and Wales for the years 1911, 1921, 1927, 1935.
† Adjusted to population of England and Wales, 1901.
‡ Data not available.

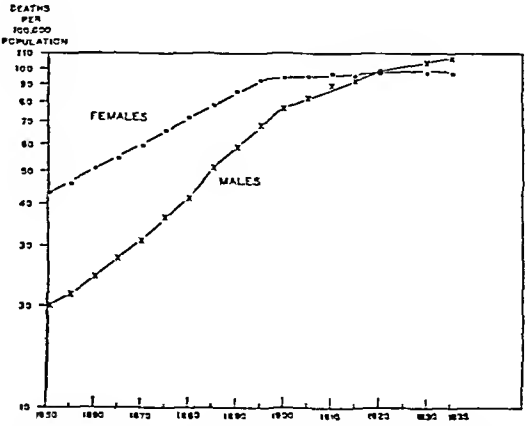

FIG. 1. *Cancer mortality in England and Wales, 1850-1937, age-standardized to population of England and Wales, 1901.*

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a tendency to decline. The increase among males, however, continued, again at a somewhat slower rate, so that if the two curves of mortality in Massachusetts continue their present trends, the rate in males will, within the next five years, exceed that in females, as in England (Table 2 and Fig. 2).

A striking feature of cancer mortality in the past century, then, has been its different course in the two sexes. One possible explanation of this difference is that, since 1915, any improvement in cancer diagnosis in females has been counterbalanced by improvement in cure rates; whereas, in males, the improvement in diagnosis was not so counterbalanced because only a small proportion of cancer in males occurs in accessible sites that have relatively high curability.

TABLE 2

CANCER MORTALITY IN MASSACHUSETTS BY SEX, 1850-1945

Average Annual Rates (Age-Standardized)* for Five-Year Periods

Mid-year of 5-yr. period	*Rate per 100,000 population*	
	Male	*Female*
1850	14.5	21.3
1855	16.7	28.7
1860	19.6	39.2
1865	19.9	40.2
1870	24.5	49.9
1875	24.1	53.5
1880	31.3	63.8
1885	33.6	68.9
1890	37.4	79.0
1895	43.5	86.8
1900	48.0	93.0
1905	57.1	102.1
1910	62.8	111.7
1915	74.4	121.9
1920	81.4	125.7
1925	90.8	127.9
1930	94.9	127.4
1935	103.3	126.5
1940	114.8	117.3
1943-45	119.3	116.7

* *Adjusted to population of Massachusetts, 1900.*
Source: Division of Cancer and Chronic Diseases, Massachusetts Department of Health.

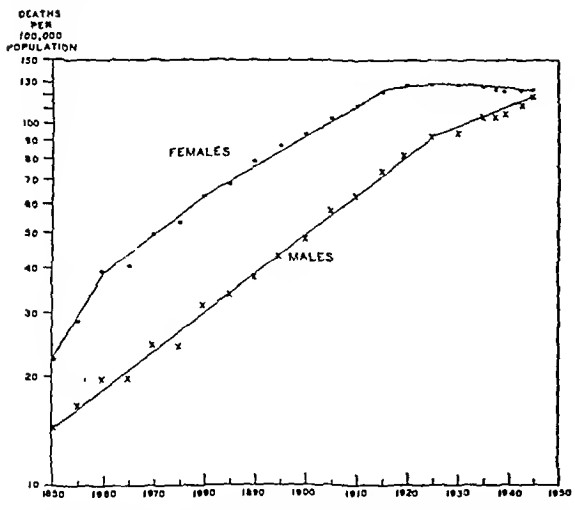

FIG. 2. *Cancer mortality in Massachusetts, 1850-1945, age-standardized to Massachusetts population, 1900.*

The chief difficulty with this explanation lies in the fact that when cancer of accessible sites and cancer of sites peculiar to sex are omitted, the difference in mortality trend in the two sexes still appears, as is indicated by the New York State data for 1931 to 1941 (Table 3). When age-standardized mortality rates for various sites of cancer are compared for the two periods 1931 to 1933 and 1939 to 1941, it is seen that sites that decreased in both sexes, decreased to a greater extent among females, and sites that increased in both sexes, increased to a greater extent among males. Cancer of sites peculiar to each sex tended to increase in males and to decrease (with the exception of "ovary and fallopian tube") in females. The net result was a decrease in cancer mortality among females of about 6 per cent, while mortality in males increased during the same period by more than 8 per cent.

Because of the different course of mortality from cancer of the same sites in males as compared to females, the possibility cannot be excluded that at least a part of the increase among males is real and not due to improved diagnosis. Further study of this possibility presents a challenge to epidemiological investigation.

We are not likely to know much more than we do now about the true trend of cancer mortality ten years hence unless, in the interim, we can obtain more information regarding the causes of death. This information could be obtained if hospitals would attempt not only to increase the percentage of autopsies performed on hospital deaths but, in addition, would try to secure autopsies in as *representative* a sample of deaths as possible. The same percentage of autopsies, as are now obtained, if secured on a random sample of deaths instead of "interesting" or problem cases, would, over a ten-year period, provide

accurate data regarding the true trend of mortality from cancer and other diseases, and thus provide answers to some of these questions.

A complete account of the epidemiology of cancer in man should go on from a discussion of the trend in time to a description of the differential incidence with respect to such

TABLE 3

CANCER MORTALITY*

New York State (Exclusive of New York City)
1931-33 and 1939-41

	Mortality Rates					
	Male			*Female*		
	1931-33	*1939-41*	*% Change*	*1931-33*	*1939-41*	*% Change*
"Nonsexual" Sites						
A. Sites decreasing in both sexes:						
Lip	1.20	1.17		0.13	0.11	
"Other buccal"	3.62	3.31		0.96	0.59	
Stomach	30.12	23.50		22.19	15.59	
Liver and biliary passages	8.82	5.79		13.11	8.02	
Skin	3.61	3.04		2.21	2.08	
Bladder	6.91	6.50		3.37	3.11	
"Other and unspecified sites"	5.61	5.55		5.84	5.34	
TOTAL	59.89	48.86	—18.4	47.81	34.84	—27.1
B. Sites increasing in both sexes:						
Mouth	0.85	1.00		0.14	0.21	
Intestines	12.99	14.88		18.53	19.33	
Rectum and anus	7.36	10.26		6.96	8.19	
Pancreas	3.15	5.36		3.48	4.39	
Mesentery and peritoneum	0.59	0.83		0.96	1.05	
Digestive organs—"unspecified"	0.16	0.18		0.18	0.31	
Lung and "other-respiratory"	4.68	11.61		2.51	3.35	
Kidneys and adrenals	1.98	2.87		1.49	1.83	
Bones	1.65	2.01		1.58	2.00	
Brain	0.81	2.09		0.70	1.25	
TOTAL	34.22	51.09	+49.3	36.53	41.91	+14.7
C. Sites increasing in males, decreasing in females:						
Tongue	1.62	1.77		0.33	0.32	
Esophagus	3.52	4.01		1.17	1.03	
Larynx	1.97	2.74		0.42	0.25	
TOTAL	6.84	8.57	+25.2	1.92	1.60	—16.7
TOTAL "NONSEXUAL" SITES	100.95	108.52	+ 7.5	86.26	78.35	— 9.2
"Sexual" Sites						
D. Male						
Prostate	12.27	14.76				
Testes	0.90	1.08				
Other male genitourinary organs	0.61	0.50				
TOTAL (male sexual sites)	13.78	16.34	+18.6			
E. Female						
Breast				29.30	30.63	
Uterus				31.08	26.29	
Ovary and fallopian tube				5.62	7.92	
Other female genital organs				0.33	0.06	
Vagina and vulva				1.12	1.46	
TOTAL (female sexual sites)				67.45	66.36	— 1.6
TOTAL "SEXUAL" SITES	13.78	16.34	+18.6	67.45	66.36	— 1.6
TOTAL ALL SITES	114.96	124.96	+ 8.7	153.71	144.70	— 5.9

* Age-standardized rates per 100,000.

factors as age, sex, race, habits, previous disease, associated disease, occupation, heredity, and other characteristics that may appear significant. This would naturally be followed by an attempt to correlate whatever differences appear with what is known regarding the etiology of malignant tumors.

Such an account might consider the malignant tumors either as a group or each individual type of malignant tumor separately. No very full account by either of these approaches is possible in a single paper. The purpose here is to discuss a few features of the epidemiology of cancer that appear to be of interest, including the relationships to age, sex, social class, carcinogenic chemicals and radiations, heredity, and the precancerous lesions. Available information regarding many of these factors is far from adequate, and often the chief conclusions to be drawn are those regarding the direction that further study might take.

Those concerned with some phase of a cancer program, directed toward providing improved diagnostic or treatment facilities for cancer, are especially interested in its epidemiological features, because even a large-scale effort at education or case finding is necessarily limited in the number of people it can reach. Obviously, such efforts will be more efficient to the extent that they are directed toward those people who present the greatest risk of developing cancer.

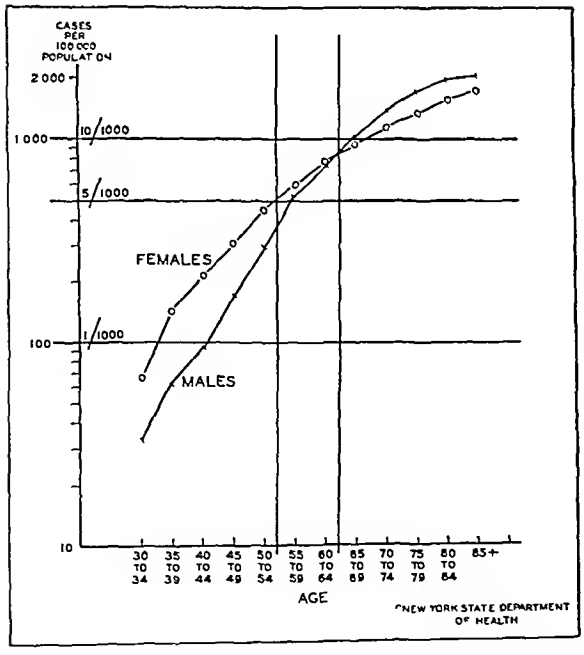

FIG. 3. *Cancer, all sites. New cases per year per 100,000 population by age and sex. New York State, exclusive of New York City, 1942-1944.*

EPIDEMIOLOGICAL FACTORS

Age. The most obvious and best-known increased risk of developing cancer is that related to age (Fig. 3). In the New York State data, which relate not to mortality or selected hospital statistics, but to all reported cases of cancer, the incidence of cancer of all sites continues to increase up to the age of 85 years, after which it tends to level off.

Several sites of cancer exhibit two or three age periods of increased incidence. For example, the leukemias, kidney tumors, and tumors of the eye show peaks at ages less than 5 years and at age 80; brain tumors at less than 5 years and at age 50; malignant bone tumors at 10 years and at 80 years of age; testicular tumors at 25 years and 85 years. These observations are of interest because they indicate that even tumors that are relatively more frequent in early life continue to increase in incidence with increasing age.

The association of cancer with age has obvious implications in diagnosis and in diagnostic case-finding procedures. For example, there has developed recently a considerable demand for the type of service called variously "cancer prevention," "cancer detection," "health maintenance," or "cancer case finding." This is essentially a more or less thorough physical examination, which may include various laboratory examinations, of persons who are apparently well. Unfortunately, the supply of such services, at least in organized clinics, does not begin to meet the demand, with the result that all such clinics now have long waiting lists, and usually their prospective clients are given appointments six months or more ahead.

The maximum possible effectiveness of such examinations in discovering otherwise unsuspected cancer in persons selected at random is indicated in Fig. 3. This shows the number of new cancer cases per 100,000 population which may be expected to occur at various ages within one year. In tuberculosis, case

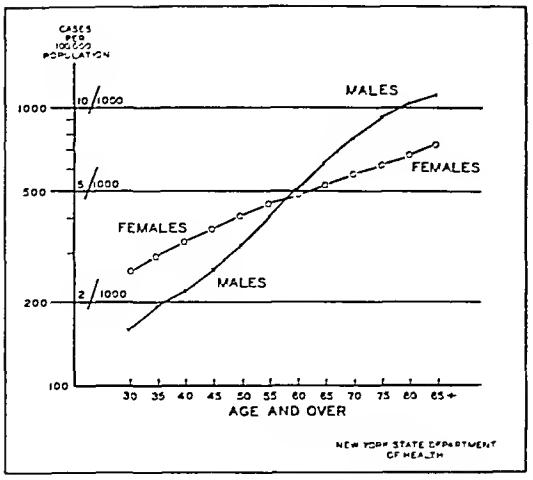

FIG. 4. *Cancer of "accessible" sites. New cases per year per 100,000 population at various ages and over. New York State, exclusive of New York City, 1942-1944.*

finding by mass roentgenographic examination, the average number of "positive" roentgenograms found in New York State, has been approximately 5 per thousand. If we take this figure as an index of what is economically feasible in cancer detection, such a number of positive examinations for cancer, assuming the complete effectiveness of such examinations, could not be expected to occur in persons less than the age of 40 years. Moreover, many forms of internal cancer would be impossible to detect at an early stage by an ordinary examination. If we consider only forms of cancer fairly accessible to inspection and palpation, then we might possibly find 5 per thousand at age 60 and over, but not at earlier ages, as is indicated in Fig. 4. Reports on the results of a year's examinations made in several cancer-detection clinics in Philadelphia shows that of 2552 persons examined, 14 were found to have cancer, or 5.5 per thousand. Since the average age of those examined was approximately 40 years, either the examinations were remarkably successful or those examined included some persons who were ill and not representative of the average population. There are, of course, factors other than age that would determine whether or not an early tumor could be discovered at a single examination and it is not my purpose to suggest that such examinations be confined to any age group. However, as long as our facilities for making examinations are limited, we may be certain that these examinations would be more effective in reducing mortality from cancer if they were made available first to the older age groups. As the data in Table 4 indicate, the effectiveness probably would be six to ten times as great in males and about two-and-a-half times as great in females, at ages 50 and over, as compared with younger ages.

In making periodic examinations, we may contemplate the use of special techniques directed toward a single form of cancer. An example would be the use of vaginal smears to discover early uterine cancer. Here other factors, in addition to age, may prove useful as guides to what groups of women should be studied most intensively. Numerous studies have shown that uterine cancer occurs more frequently among married than among single women. Also, it is approximately three times more frequent among women who have had syphilis,[8] and it is almost twice as frequent among Negro women as among white. Randall has demonstrated that women whose menopause is characterized by a period of menorrhagia suffer an increased incidence of carcinoma of the uterine fundus in later life. Thus, although no woman can be character-

TABLE 4
EFFECT OF AGE ON CANCER CASE FINDING*

	New cases expected per 1000 examined per year					
	Males		*Females*		*Ratio of 50 yrs./30-49 yrs.*	
	30-49 yrs.	*50 yrs. & over*	*30-49 yrs.*	*50 yrs. & over*	*Males*	*Females*
All cancer	1.0	6.4	2.2	6.5	6.40	3.00
"Accessible" cancer	0.3	3.2	1.5	4.0	10.00	2.66

* Based on incidence of reported cases, New York State, exclusive of New York City, 1942-1944.

ized as free from the risk of developing uterine cancer, its increased frequency among Negroes, the married, the syphilitic, and those who have had an abnormal type of menopause indicates that the greatest number of new cases among each 100 examined would be found in such groups and points to the desirability of directing case-finding efforts most intensively toward these groups.

Precancerous Lesions. Perhaps the most important sphere of activity with regard to case finding and the prevention of cancer is that directed toward the detection of the so-called precancerous lesions. The concept of a "precancerous" lesion is essentially a statistical one, since it indicates an increased probability of developing cancer. The term "precancerous" has been applied to some forty-five different pathological conditions. More than a third of these are in the skin, including radiation and actinic dermatitis, senile and arsenical keratosis, xeroderma pigmentosum, lupus vulgaris—especially if previously treated by irradiation—neuronevi, chronic osteomyelitic sinus tracts, burn scars, erythroplasia, and chronic atrophic acrodermatitis.

In the buccal, oral, and pharyngeal mucous membranes, the recognized precancerous lesions are leukoplakia, luetic glossitis, and the Plummer-Vinson syndrome; in the gastrointestinal tract—gastric, intestinal, and rectal polyps, and myomas; in the salivary glands—the mixed tumors; in the uterine fundus—endometrial hyperplasia and endometrial polyp; in the vulva—kraurosis vulvae; in the liver—cirrhosis; in the breast—cystic and atypical proliferative hyperplasia of the ducts and lobules; in the ovary—cystoma and dermoids; in the testis—the cryptorchid, inguinal, or intra-abdominal testis; in bone—Paget's disease, giant-cell tumors, chondroma, and Albright's syndrome; in the soft tissues—neurofibromatosis, myxolipoma, and deep plexiform neuroma; in the bladder—papilloma; in the gallbladder—calculous cholecystitis; and in the thyroid—nodular goiter and probably fetal adenoma. Certain general diseases connote an increased cancer risk in certain organs; in diabetes—cancer of the pancreas; in pernicious anemia—cancer of the stomach; and in syphilis—cancer of the tongue in males and of the uterine cervix in females. In many instances the precise risk of cancer which these conditions imply has not been determined accurately.*

The further study of suspected precancerous conditions, to determine the precise statistical risk of developing into cancer that they carry, is a matter of considerable importance, because only in this way can convincing evidence of the precancerous significance of these lesions be collected. For example, the relationship of so-called chronic cystic mastitis to breast cancer was obscured for many years by studies that failed to take into account the age of the patients studied and the length of the period of observation. With the appearance of the work of Warren and more recently of Foote and Stewart showing that the subsequent incidence of breast cancer in women with cystic mastitis is about five times the average, the precancerous nature of these lesions has been established, with the result that they are being treated with the respect they deserve. Here is another field for the epidemiological study of cancer.

Although these and other epidemiological relationships of cancer are well known and have practical applications in control, very few of them can be explained by observations thus far made in the laboratory on carcinogenesis. Indeed, the epidemiological study of cancer discloses as many mysteries as does clinical or laboratory investigation. A simple but striking example is the relative incidence of cancer of the same site in the sexes. Cancer of the larynx and the lip are from ten to fourteen times as frequent among males as among females. Cancer of the mouth, tongue, pharynx, and esophagus are three to four times as frequent among males. The two sites of cancer that show an opposite selection are the gallbladder and the thyroid, respec-

* There is a tendency in published observations on this point to confuse frequency of association with cancer incidence. For example: cancer of the tongue in males is associated with luetic glossitis in from 20 to 30 per cent of cases. This, obviously, does not mean that 20 to 30 per cent of male syphilitics develop tongue cancer. The actual incidence is about five times the normal or average. Since the average incidence of tongue cancer throughout life is less than 2 per thousand, the cumulated incidence of tongue cancer in male syphilitics throughout life is approximately 1 per cent.

tively twice and four times as common in women as in men. These sex differences in cancer incidence can hardly be explained by difference in diagnostic accuracy, since it is difficult to understand why cancer of the same site should be diagnosed more readily in one sex than in the other.

Socio-economic Position. Differences in cancer mortality between socio-economic groups, such as have been observed in this country and in England, are similarly difficult to explain. The observations, in brief, are that mortality is highest in the unskilled worker group and lowest among professional workers. Further analysis shows that these differences do not hold for all sites of cancer, but are found in males chiefly in cancer of the skin, larynx, the oral cavity, the pharynx, the esophagus, and stomach—and in females, in these sites and in the uterus. Breast cancer, on the other hand, is apparently most frequent in women of the highest economic groups, who also have the lowest birth rate. These observations are at least suggestive that there may be factors associated with social and economic status that are significant in the causation of malignant tumors. Certainly they indicate the desirability that epidemiological investigations of cancer should include a study of social and economic factors to determine whether these differences are real or only apparent.

Carcinogenic Chemicals and Radiations. The most obvious approach of this kind would be directed toward discovering possible occupational exposure to carcinogenic chemicals or to radiations, whether ultraviolet or shorter wave lengths. A study of occupational hazards in this country shows that there are approximately two hundred different trades or occupations that involve possible exposure to carcinogenic radiations or chemicals, including arsenic, tar, petroleum products, benzol, aniline compounds, roentgen rays, ultraviolet radiation, radium, nickel carbonyl, and chromates.

One of these "cancerigenic occupations" is that of the roentgenologist. It is well known that a good many of the physicians who pioneered in radiology later developed radiation dermatitis of the skin of the hands, with the subsequent development of squamous-cell carcinoma. Thus, fourteen years after the discovery of roentgen rays, Hesse was able to collect ninety-four cases of roentgen-ray cancer of the skin, fifty of them in physicians. Haagensen, in 1931, reported eleven cases in physicians seen at Memorial Hospital in New York City. This hazard has been eliminated largely by suitable methods of protection. However, it has now been shown that leukemia, which can be produced experimentally by irradiation, occurs about ten times as frequently in radiologists as in the general population. Since radiology is a relatively young specialty, most of the radiologists who have developed leukemia thus far probably were in practice during the period when protective devices were not as well developed as they are now. That a constant and systematic search for new possible sources of exposure to carcinogenic agents is needed is indicated also by a recent observation that during the process of manufacture of electronic tubes, roentgen rays are produced in a concentration considerably above the 0.1 r which has been considered the maximum, safe, daily dose.

The two great difficulties in the investigation of the relation between human cancer and carcinogenic agents are the long "incubation period" of malignant tumors, and the fact that, thus far, we cannot distinguish histologically between a tumor produced by a known carcinogenic agent and one which apparently arises spontaneously. The long "incubation period" of induced tumors makes it probable that many such tumors occurring as a result of occupational exposure do not appear until after the worker has retired or changed his occupation. Although industries, such as the aniline-dye industry in which a known carcinogenic hazard occurs, institute protective precautions and periodic examinations, the need for continuing these examinations after the worker leaves the occupation is not always recognized. At any rate, despite the large number of occupations in which exposure to carcinogenic agents may occur, only a small number of cases of occupational cancer have been reported, perhaps eight to nine thousand in all countries, of which ap-

proximately four hundred cases have been reported from the United States.[7] The most promising field for further investigation of the relation of carcinogenic chemicals and radiations to human tumors would seem to lie in epidemiological studies of large numbers of persons who are or have been engaged in occupations in which exposure to these agents may occur. Since the clinical course and the therapy of a malignant tumor are much the same regardless of how it has been produced, the significance of such studies would be confined to the possibility of prevention and early case finding.

Hereditary Factors. The important contributions of Bittner and others in the study of breast cancer in mice and its relation to a virus-like factor found in the milk and tissues of breast-cancer–strain mice have focussed attention on the possibility that breast cancer in humans may have a similar cause. The established epidemiological facts regarding breast cancer in humans are that it occurs most frequently in single women and that it is associated in approximately 50 per cent of cases with pre-existing cystic or atypical proliferative hyperplasia of the breast ducts or lobules. These two conditions may be related, since cystic proliferative mastitis is said to be most common in women who have never borne children. In addition, there is suggestive but not conclusive evidence of a familial relationship to the effect that the daughters of a mother who had breast cancer are also more likely to develop breast cancer.

If human breast cancer is caused by a virus-like factor occurring in human milk, then the disease would be rare in women who had never been nursed in infancy, rare in women whose mothers had not developed the disease, and common in women whose mothers had developed it. A review of the literature to date does not show any evidence regarding the first two points and only suggestive evidence of the last. We are thus scarcely in a position as yet to advocate that all mothers be advised not to nurse their female infants, in order to prevent the occurrence of breast cancer in the next generation.

Prior to the discovery of the milk factor, breast cancer in the mouse was considered an excellent example of the genetic causation of cancer. The discovery of the milk factor reduced but did not eliminate the importance of the genetic or other factors in the etiology of breast cancer in mice. In humans, the available evidence regarding genetic factors in cancer comprises, first, the existence of a few tumors and precancerous conditions that are apparently hereditary, including retinoblastoma, xeroderma pigmentosum, familial intestinal polyposis, and multiple neurofibromatosis; second, the undeniable existence of so-called cancer families in which a high percentage of the blood relatives in the family develop some form of malignant tumor. The true number of such families is unknown but about a hundred have been described.

The best statistical studies on this question have been those made in this country by Lombard, utilizing death-certificate data, and by Crabtree, using very carefully obtained histories of patients with histologically proved cancer. These studies show that the parents, siblings, and children of cancer patients do have more cancer than would be expected—approximately 30 per cent above the average. The increase is apparently most marked in the families of patients who develop cancer relatively early in life. These studies suggest that cancer incidence does tend to concentrate in certain families, but not markedly. Indeed, the entire increase observed in one of these studies could be accounted for by an increase of one case or more in less than 10 per cent of the families studied.

Heston has pointed out that hereditary and constitutional factors in human cancer probably occur, as is true of the more fundamental inherited body traits, in the form of what the geneticists term "multiple factors," which means that their influence can be manifested in widely varying degrees. At any rate, this hypothesis would account for the observed facts of familial occurrence in a few families with relatively weak predisposition in the majority of persons that probably requires special environmental or functional stimuli to become effective.

We do not as yet have sufficient evidence regarding parental influence in human cancer to consider the occurrence of cancer in

one member of a family as the signal for examination and continued follow-up of the patient's brothers and sisters. This procedure would be indicated in the case of identical twins; if the tumor was of a type known to be hereditary, such as retinoblastoma; or if the family was known to be prone to cancer. In some clinics, a family history of breast or uterine cancer is considered significant in determining the need for special care in searching for a tumor of these sites in the patient.

The precise role of hereditary factors in the causation of human cancer, and the extent to which such factors are modified by environmental influences, remain obscure. There is little doubt that such factors do exist for some tumors and in some families, but the available evidence indicates that they are of minor importance in most cases.

Summary

The occurrence of human cancer is in some cases attributable to the effect of various chemical and physical agents; in others to the previous presence of precancerous lesions and other diseases, in a relatively small number of cases to familial or hereditary influences. In the great majority of cases, no one of these etiological factors can be identified. Considerable differences appear in the incidence of certain forms of cancer in the two sexes and in persons of different race and economic status. Most of these differences, although not explicable by any theories yet advanced regarding the causation of cancer, do, however, point to possible applications in the form of special attention in education, case finding, and continued observation paid to those groups that apparently have an increased incidence of certain forms of the disease. The experience already gained in a few clinics, in case finding among apparently healthy persons, indicates that the number of cancer cases discovered in this way is comparable to that of early cases of tuberculosis found by mass roentgenographic examinations If active, case-finding procedures be applied to the groups that, on epidemiological grounds, show higher than normal cancer incidence, we may expect such procedures to be correspondingly more effective Finally, the need to test and extend these observations further by including systematic studies in the epidemiology of this disease in the rapidly expanding program of cancer research is indicated

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NATIONAL RESEARCH COUNCIL APPOINTS SUBCOMMITTEE ON ONCOLOGY

THE Committee on Pathology of the National Research Council has appointed a Subcommittee on Oncology.

The members are:

Dr. Shields Warren, Chairman
Dr. Balduin Lucké
Dr. Fred Stewart
Dr. Harold Stewart
Dr. Arthur P. Stout
Dr. Milton C. Winternitz
Dr. Howard T. Karsner, Chairman of Committee on Pathology, ex officio

Brig. Gen. Raymond C. Dart, Director of the Army Institute of Pathology, is cooperating with the Committee and making the Institute's facilities and resources available and is providing office space for the permanent secretary.

The objectives of the Subcommittee are:

1. Improvement in the teaching of oncology;
2. Dissemination of information on oncology to clinical pathologists, students, and teachers of oncology;
3. The establishment of criteria for diagnosis of tumors;
4. The simplification of terminology by recommending a single term for each tumor and listing separately the appropriate synonyms.

The Subcommittee expects to work with existing agencies to promote clarity and unity in tumor nomenclature and classification.

I. H. PERRY, M.D.
Exec. Sec., Subcommittee on Oncology

Army Institute of Pathology
Washington 25, D. C.

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1.3%; all others, 24.0%. Tables of age distribution, anatomical incidence, treatment delay, and survival are given and discussed. An encouraging trend is shown in the comparison of the 25.0% 5-yr. survival of 815 traced, living individuals, microscopically proved to have cancer, treated in 1935, and 39.6% of 1376 treated in 1941.—*D. A. S.*

Mahadevan, R. [Erskine Hosp., Madura, India]: **Early diagnosis of malignant growths with a brief reference to their incidence in India.** J. Indian M. A. 17: 1-7, Oct., 1947.—Of 1089 cases of malignant tumor proved by biopsy and collected from various hospitals in India, 86.2% were carcinomas and 13.8% sarcomas. Of the carcinomas, 62.2% were obviously visible or within reach of the examining finger: mouth, 175; male reproductive organs, 171; cervix and vulva, 91; breast, 113; rectum, 45; skin, 90. Points of contrast with European and American populations are the low incidence of carcinoma of the stomach (only 3.5%) and of the lung. The author believes that some differences in incidence may be explained by the fact that the average life span in India is only 26 yrs.—*D.A.S.*

Morel, A., & Josserand, A.: **A propos de quelques notions de cancérologie contemporaine. Déductions théoriques et pratiques. [Some current views on cancer. Theoretical and practical deductions.]** J. de méd. de Lyon 29: 75-80, Feb. 5, 1948.

Parker, George L. [Norfolk, Mass.]: **The Pondville State Cancer Hospital, 1927-1947.** New England J. Med. 238: 800-805, June 3, 1948.

Taffel, Max [Yale Univ. Sch. Med., New Haven, Conn.]: **The utilization of a university cancer clinic for teaching purposes.** Connecticut State M. J. 12: 532-535, June, 1948.

Whipple, Allen O. [New York City]: **Clinical training in the diagnosis and treatment of cancer.** Pennsylvania M. J. 51: 976-981, June, 1948.

Willis, R. A.: **Pathology of Tumours.** St. Louis. C. V. Mosby Co. 1948. 992 + [52] pp. $20.00.—Dr. Rupert A. Willis is now pathologist of the Royal Cancer Hospital (Free) in London. He was formerly the pathologist of the Alfred Hospital, Melbourne, Australia, and until very recently the Sir William H. Collins Professor of Human and Comparative Pathology of the Royal College of Surgeons. His profound interest in the pathology of cancer is very well known to American oncologists from his many interesting papers and especially from his valuable monograph on "The Spread of Tumours in the Human Body." Now he has undertaken to cover the entire field of the pathology of human and animal tumors in a single volume of 992 royal octavo pages. The first 207 pages consider definition, nomenclature, malignancy, experimental production, statistics, animal tumors, the structure, function, growth, spread and metastasis of tumors, and the hypotheses of neoplasia. The other 786 pages deal with tumors on a regional basis and with special tumor forms such as teratomas. The body of the text is preceded by 23 pages of preface, table of contents, and list of illustrations, and is succeeded by 52 pages of index. There are 500 splendid illustrations, almost all of which are black and white reproductions of photomicrographs very carefully chosen and truly illuminating. The book is addressed primarily to pathologists and its chief value will be as an aid to the histological recognition and accurate labeling of tumors. The author is an individualist with an orderly mind, strong convictions based upon personal observations chiefly at the autopsy table, a lucid and entertaining style, and the belief that having displayed the opinions of others regarding a controversial subject he should give vigorous expression to his own. These attributes make the book lively and entertaining, which is certainly a source of gratification. They also contain the germ of its weaknesses. Twenty years as pathologist at the Alfred Hospital and elsewhere cannot possibly furnish enough tumor material to permit Dr. Willis to qualify as an expert on all subjects concerning neoplasia, especially when, as sometimes occurs, he is willing to controvert the opinions of others on the basis of a very small personal experience. For example, in discussing the subject of Abrikossoff's myoblastic myomas, he expresses the conviction that they are neither myoblastic nor neoplastic, and then tries to make this position impregnable by intimating that if true neoplasms with this appearance should exist they should be called by another name. He devotes nearly 6 pages and 4 illustrations to this relatively minor topic and the casuistry of some of the discussion suggests that his enthusiasm for polemics tends to upset his scientific judgment. Another subject on which the author maintains a stubborn resistance to the weight of evidence concerns primary growths of peritoneum and pleura, the existence of which he doubts because he himself has never recognized an example. He is apparently unaware that the mucoid material secreted by these tumors is hyaluronic acid and not mucus or pseudomucin, a fact far more important than any morphological evidence for believing in their occurrence. This stubborn refusal to accept the possibility of a primary mesothelial growth has apparently been the cause of the only example of what this reviewer believes is mislabeling in the book. Figure 347 is called a lymphangioma of the epididymis, although it resembles exactly the so-called benign mesotheliomas of that organ described by Masson, Evans, and others. Apparently the author is unacquainted with their papers. It seems that the development of the recognition of malignant tumors by the cytological examination of secretions and excretions had not attained the widespread use now current in this country when this book was compiled so that it receives scant attention. This is probably just as well for it is still in the developmental stage and its practice is far from established on a firm basis. This reviewer feels that the book would be far more useful to a greater number if the author had devoted less space to debate and such subjects as experimental cancer and tumors in animals

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and more to an integration of pathology with clinical medicine and treatment. But perhaps it is fortunate that he did not, for, on the rare occasions when he does so, his conclusions are sometimes open to question, for example, in the recommendation that all cases of benign papillary tumors of the female breast be treated by simple mastectomy.

These critical comments are not intended to detract from the sterling qualities of the book. In general, Dr. Willis is a close and careful student and when his judgment is not warped by prejudice his observations are sound and searching. This reviewer has only admiration for his splendid discussions of such subjects as nomenclature, statistics, the myth of tumor implants on intact epithelial surfaces, and many, many others. There is an enormous amount of factual information for the pathologist stored within its covers, admirably documented, splendidly illustrated, and so well indexed that one loses no time in finding all references to any given subject. While it would be improper to depend upon this volume alone to furnish the necessary basis for the diagnosis of cancer, it must be considered an indispensable part of every laboratory and clinic dealing with the diagnosis, treatment and investigation of tumors. *A. P. Stout, M.D.*

CANCER CONTROL

Anon.: The cancer program in New Jersey. Part IV. Financial aid for services to cancer patients. J. M. Soc. New Jersey 45: 226-234, May, 1948.

Anon.: Program of the Field Army. American Cancer Society, New Jersey Division, Inc. J. M. Soc. New Jersey 45: 298-300, June, 1948.

Candel, Perihan: Cancer control in Turkey. J. Am. M. Women's A. 3: 165-166, Apr., 1948.

Cameron, Charles S. [Am. Cancer Soc., New York City]: Cancer control in the United States. J. Am. M. Women's A. 3: 166-168, Apr., 1948.

DeLawter, DeWitt E. [Nat. Cancer Inst., Bethesda, Md.]: Culpability for the delay in the management of cancer. M. Ann. District of Columbia 17: 342-346; 369-370, June, 1948.

Gamble, H. A. [Greenville, Miss.]: The problems of *cancer and cancer clinics*. Mississippi Doctor 25: 305-308, May, 1948.

Helse, Agnete: The Danish Anti-Cancer League. Organization and undertakings. J. Am. M. Women's A. 3: 164-165, Apr., 1948.

Knowlton, Isabel [Strang Cancer Prev. Clin., New York City]: Education. J. Am. M. Women's A. 3: 145-146, Apr., 1948. Brief discussion of the cancer-prevention education needed by the medical profession and laity. *D. A. S.*

Kaplin, Allen N. [Nat. Cancer Inst., Bethesda, Md.]: Objectives and program of the Arkansas cancer detection project. Pub. Health Rep. 63: 813-821, June 18, 1948.

Sowder, Wilson T. [Jacksonville, Fla.]: Cancer control in Florida. J. Florida M. A. 35: 23-27, July, 1948.

Teittinen, Aino: Cancer control in Finland. Group examination of women. J. Am. M. Women's A. 3: 163-164, Apr., 1948.

Wells, A. H.: A new cancer educational service. Minnesota Med. 31: 671, June, 1948.

Zuckermann, Conrado: El médico general en la lucha anticancerosa. [The general physician in the campaign against cancer.] Rev. méd. veracruzana 27: 1516-1519, Oct., 1947.

INDUSTRIAL CANCER

Hill, A. Bradford, & Faning, E. Lewis: [London Sch. Hyg. & Trop. Med., Eng.]: Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic. I. Mortality experience in the factory. Brit. J. Indust. Med. 5: 2-6, Jan., 1948. The factory workers whose mortality experience has been analyzed show in their deaths recorded in 1910–13 a proportional and significant excess of deaths attributed to cancer when compared with 3 other occupational groups living in the same area. The deaths of the former include 29% attributed to cancer, and the latter 13%. Standardization for age and period of time does not materially affect this comparison. A proportional excess of cancer in the factory workers, and of much the same order, is consistently apparent in each of the 3 periods 1910–19, 1920–29, and 1930–13. It is present at ages under 55 and 55–69 but is small and insignificant at ages 70 and above. The proportional excess is confined to workers in the chemical processes, including engineers and packers, and is entirely absent from a general group of operatives in the same factory, such as painters, box-makers, etc., who would be unlikely to be exposed to any specific hazard. The numbers are small when subdivided by the site of growth, but there is a suggestion in the figures that the factory workers have been especially affected in the lung and skin. *Auth. Concl.*

Perry, Kenneth; Bowler, R. G.; Buckell, H. M.; Druett, H. A., & Schilling, R. S. F. [London Hosp., Eng.]: Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic. II. Clinical and environmental investigations. Brit. J. Indust. Med. 5: 6-15, Jan., 1948. Workers exposed to arsenic dust were found to have a higher content of arsenic in their hair and to excrete on the average more arsenic in their urine than control workers not so exposed. The scatter of these observations, however, is very wide, and a single observation in a given individual is not informative. Clinically the workers manifest gross pigmentation, with hyperkeratinization of exposed parts with a tendency to wart formation. No worker was found who had carcinoma of the bronchus, but since the trachea and bronchi must be exposed to the same dust as the skin, and since they are lined by a modified squamous epitheli-

um, it is only natural to expect that they would undergo the same changes. After many years' exposure, a squamous-cell carcinoma may develop in the bronchus. Two cases were seen in which warts had become malignant and had been treated with radium. Thus, while no concrete evidence was found to confirm the statistical findings of the mortality investigation, there was circumstantial evidence to support these findings in the form of clinical observations of skin changes in all the arsenic workers.—*Auth. Concl.*

ETIOLOGY AND PATHOGENESIS

Augusto, Picco [Turin, Italy]: **Influenza della follicolina sullo sviluppo degli innesti embrionali. [Influence of folliculin on the development of embryonal rests.]** Tumori 21 (4/5): 204-212, 1947.

Jacob, P. [Centre anticancéreux de Lorraine, France]: **Une conception évolutionniste de la genèse et du comportement des tumeurs. [An evolutionary theory of the genesis and behavior of tumors.]** Rev. méd. Nancy 72: 355-359, Dec. 1/15, 1947.

Kidd, John G. [Cornell Univ. M. Coll., New York City]: **Viruses and virus-like agents as causes of cancer. A brief recounting and reflection.** Bull. Johns Hopkins Hosp. 82: 583-600, June, 1948.

Lang, C. A. [Osp. Riuniti, Trieste, Italy]: **Neuer Beitrag zur Erforschung der geographischen Bedingungen bei der Krebssterblichkeit. [A further contribution to the study of the geographic factors in cancer mortality.]** Schweiz. med. Wchnschr. 78: 13, Jan. 10, 1948.—The cancer mortality from 1900 to 1939 was the same in a standardized population of Dutch in Holland and Dutch immigrants to the Dutch East Indies, pointing to the dominance of the genetic over the geographic factor. (Schinz, Rosin, and Senti had earlier suggested that the high cancer mortality in the Alpine regions of Europe was due to geographic factors.)—*M.C.J.*

Lang, C. A. [Osp. Riuniti, Trieste, Italy]: **Ueber die Möglichkeit eines Einflusses der Alpenkette auf die Krebssterblichkeit. [Possible influence of the Alpine chain on cancer mortality.]** Schweiz. med. Wchnschr. 78: 233, Mar. 13, 1948.—The cancer mortality from 1913 to 1939 was the same in a standardized population of Italians in Italy and Italian immigrants to Libya, again pointing to the dominance of the genetic over the geographic factor.—*M. C. J.*

Pinck, Louis A. [Bethesda, Md.]: **A biochemical hypothesis of the genesis of cancer.** Ann. New York Acad. Sc. 50 (1): 1-17, 1948.—A hypothesis of the genesis of cancer based on a correlation of chemical and carcinogenic activities of 2-acetylaminofluorene has been formulated, showing that 2-acetylaminofluorene, as such, is not carcinogenic but that it may be a precursor of the carcinogen, 2,2'-*di*(acetylamino)dibiphenylene-ethylene, which is obtained by enzymatic dehydrogenation. A chain of reactions has been formulated showing a chemical picture of the genesis of cancer involving the regeneration of the carcinogenic compound which repeats the chain of reactions on fresh cell substance. It has also been postulated that other fluorene compounds having certain substituents in the 2 and 2,7 positions may be precursors of carcinogenic compounds. Other carcinogenic representatives of the following classes of compounds have been considered: stilbenes, aromatic compounds containing a methyl group, a 5-membered ring and cyclic hydrocarbons, azo compounds, and amines. It is postulated that the reactive portion of the carcinogenic molecule is either the ethylenic or azo groups. Those compounds which do not have these configurations obtain one or the other by enzymatic dehydrogenation. It has also been postulated that the difference between cancer tissue and normal tissue is that the former consists of a very long carbon chain of cell substance. On the basis of the proposed hypothesis, some hitherto unprepared organic compounds are predicted to be carcinogenic. New lines of chemical and biological studies relating to carcinogenesis are suggested.—*Auth. Summ.*

Wiesslien, Bessie G. [Mt. Sinai Hosp., Cleveland, Ohio]: **The role of sex hormones in the pathogenesis and treatment of cancer.** J. Am. M. Women's A. 3: 186-188, May, 1948.

DIAGNOSIS

Abderhalden, Emil [Martin Luther-Univ., Halle, Germany]: **Lassen sich verschiedenartige Störungen des lymphatischen Systems mittels der A.-R. unterscheiden? [May various disturbances of the lymphatic system be differentiated by protective proteinases?]** Ztschr. f. Vitamin-, Hormon- u. Fermentforsch. 1 (3/4): 289-295, 1947.—It was found that after parenteral administration [to rabbits] of carcinoma or of lymphosarcoma substratum, protective proteinases appeared in the urine that hydrolyzed only the particular substratum. The reactions were not uniform in disturbances of the lymphatic system, but a strongly specific reaction was obtained with leukemic-myelosis tissue.—*Auth. Summ.*

Bogatko, Frances H., & Bader, Genevieve M. [Strang Cancer Prev. Clin., New York City]: **Statistical report for 1946. The Kate Depew Strang Prevention Clinic of Memorial Hospital (Women's Division).** J. Am. M. Women's A. 3: 132-134, Apr., 1948.—In 1946, 37 cancers were discovered (cervix uteri 11, breast 10, rectum 7, fundus uteri 3, ovary 1, stomach 1, kidney 1, skin 2, retroperitoneal sarcoma 1) in 3564 patients, an incidence of 1.03%. Tables are presented of age distribution, sites of cancers, marital status, family history, special examinations, precancerous lesions, other diseases, and previously diagnosed and treated cancers.—*D. A. S.*

Ekstrom, Dorothy [New York Infirmary, New York City]: **Statistical report for 1946. The**

Strang Cancer Prevention Clinic of the New York Infirmary. J. Am. M. Women's A. 3: 132, Apr. 1948.—In 1946, 19 cancers were discovered (sigmoid 2, skin 2, labia 1, cervix uteri 2, fundus uteri 1, breast 11)—an incidence of 1.4% in 1356 apparently healthy individuals. Tables are presented of clinic visits, age groups, site of cancers, and other diseases.—*D. A. S.*

Ewing, James H. [Strang Cancer Prev. Clin., New York City]: **Statistical report for 1946. The Kate Depew Strang Prevention Clinic of Memorial Hospital (Men's Division).** J. Am. M. Women's A. 3: 134-135, Apr., 1948.—In 1672 male patients seen during 1946, there were 16 cancers, 1.0% (basal-cell carcinoma 9, rectum 4, larynx 1, squamous-cell carcinoma 1, descending colon 1); 146 precancerous lesions, 8.7%; 253 benign tumors, 15.1%; 108 constitutional diseases, 6.5%. Tables are presented of incidence, age-group distribution, and types of cancer.—*D. A. S.*

Gallico, Edoardo [Inst. Naz. Studio e Cura dei Tumori, Milan, Italy]: **Le agglutinine a frigore nel siero dei cancerosi. [Cold agglutinins in the serum of cancer patients.]** Tumori 21 (4/5): 189-193, 1947.

Leslie, Eugenie P., & Chang, Helen [Strang Cancer Prev. Clin., New York City]: **Cytologic test of various body fluids in early diagnosis of cancer.** J. Am. M. Women's A. 3: 236-239, June, 1948.

Macklin, Madge Thurlow [Ohio State Univ., Columbus, Ohio]: **Making the doctor cancer conscious.** J. Am. M. Women's A. 3: 147-149, Apr., 1948.

Scharnagel, Isabel M. [Strang Cancer Prev. Clin., New York City]: **Diagnosis of cancer. The technique of taking biopsies.** J. Am. M. Women's A. 3: 142-144, Apr., 1948.—The necessity for surgical removal or biopsy of various skin lesions is emphasized, and the technique of aspiration biopsy described.—*D. A. S.*

Vernes, Arthur [Paris, France]: **La mesure de la maladie. Cancer. [Measure of disease. Cancer.]** Arch. internat. de neurol. 67: 1-9, Jan., 1948.

TREATMENT

Axelrod, Dorothy J., & Hamilton, Joseph G. [Univ. California, Berkeley]: **The radioautographic technique.** U. S. Nav. M. Bull. (suppl.): 122-141, Mar./Apr., 1948.

Barth, G. [Univ.-Klin. Erlangen, Germany]: **Zur Entwicklung der Tumortherapie. [The development of tumor therapy.]** Strahlentherapie 77 (2): 189-192, 1947.—A review.

Blain, Alexander, III, & Nurnberger, Carl E. [Alexander Blain Hosp., Detroit, Mich.]: **Nitrogen mustard therapy for malignant tumors; with particular reference to tumors of epithelial origin.** Alexander Blain Hosp. Bull. 7: 43-51, May, 1948.—Results of treatment of 18 miscellaneous tumors.

Boag, J. W. [Hammersmith Hosp., London, Eng.]: **The presentation and analysis of the results of radiotherapy. Part II. Mathematical theory.** Brit. J. Radiol. 21: 189-203, Apr., 1948.

Brown, W. M. Court [Roy. Infirmary, Edinburgh, Scotland]: **The value of platelet counts in radiotherapy.** Brit. J. Radiol. 21: 221-225, May, 1948.—The effect of wide-field irradiation on the blood-platelet level is described, and it is suggested that this is a more reliable indicator of the effect of radiation on the bone marrow than the total white-cell count. By using the blood-platelet level in this manner it is possible to avoid altogether the production of partial or permanent marrow failure. The use of the platelet level in the planning of treatment is described. The relationship between the development of petechial hemorrhages and radiation-induced thromboeytopenia is discussed.—*Auth. Summ.*

Catcheside, D. G.: Survey of effects of radiation on chromosomes. Brit. J. Radiol. [1947] (suppl. 1): 66-74, 1947.

Cattell, Richard B. [Lahey Clin., Boston, Mass.]: **The surgical treatment of cancer.** California Med. 68: 416-418, June, 1948.

Dodds, E. C. [Middlesex Hosp., London, Eng.]: **Oestrogens in the treatment of cancer.** Post Grad. M. J. 24: 295-298, June, 1948.

Dresser, Richard [Boston, Mass.]: **Further observations on the use of three-million-volt roentgen therapy.** Radiology 50: 645-648, May, 1948.

Finch, Ernest [Roy. Infirmary, Sheffield, Eng.]: **Treatment of cancer. The problem of organisation.** Lancet 1: 803-806, May 22, 1948.

Garai, Oliver [King's Coll. Hosp., London, Eng.]: **Nitrogen mustard.** Post Grad. M. J. 24: 307-311, June, 1948.

Horvath, J. [Univ.-Frauenklin. Erlangen, Germany]: **Morphologische Untersuchungen über die Wirkung der Ultraschallwellen auf das Karzinomgewebe. [Morphological studies on the effect of supersonic waves on carcinomatous tissue.]** Strahlentherapie 77 (2): 279-290, 1947.—It was found that the carcinoma cells were completely destroyed while the normal tissue surrounding the carcinomatous nests of cells was uninjured and only the fibers of the connective tissue showed a slight, reversible, swelling. (A basal-cell epithelioma and a squamous carcinoma were used.)—*M. C. J.*

Koller, P. C.: The effect of radiation on the normal and malignant cell in man. Brit. J. Radiol. [1947] (suppl. 1): 84-98, 1947.

Korb, Hansgeorg [Bayreuth, Germany]: **Über eine Kombination der Röntgenbestrahlung mit der Kurzwellenbehandlung. [A combination of roentgen-ray and short-wave irradiation.]** Strahlentherapie 77 (2): 301-303, 1947.—A review.

Lamerton, L. F. [Roy. Cancer Hosp. (Free), London, Eng.]: A theoretical study of the results of ionization measurements in water with x-ray and gamma-ray beams. Part I. Methods of calculation. Brit. J. Radiol. 21: 276-286, June, 1948.

Lea, D. E.: The induction of chromosome structural changes by radiation: detailed quantitative interpretation. Brit. J. Radiol. [1947] (suppl. 1): 75-83, 1947.

Martin, Hayes [Memorial Hosp., New York City]: Tracheal airway for use during total laryngectomy. Am. J. Surg. 75: 755-756, May, 1948.

Mesnil de Rochemont, R. du [Marburg, Germany]: Die Entwicklung der strahlentherapeutischen Methodik bei tiefliegenden Krebserkrankungen. [The development of radiotherapeutic methods for internal malignant diseases.] Strahlentherapie 77 (1): 1-16, 1947. —A review.

Morel, A., & Jnsserand, A.: La désinfiltration palliative des cancers par divers sels complexes ferrico-sodiques. Indications respectives des voies buccale et parentérale. [Palliative infiltration of cancers by complex ferric-sodium salts. Indications for oral or parenteral administration.] J. de méd. de Lyon 29: 89-92, Feb. 5, 1948.

Ollerenshaw, G. J. W. [Hosa Res Labs, Sunbury-on-Thames, Eng.], & Lowe, E. Cronin: 1948 report on the clinical results of H.11 therapy in cancer. M. World [London] 68: 552-559, June 25, 1948.

Trump, John G. [Massachusetts Inst. Technol., Boston]: Physical basis for the high skin tolerance of supervoltage roentgen rays. Radiology 50: 649-656, May, 1948.

Wawro, N. William [Hartford, Conn.]: Experience with the use of nitrogen mustard at the Hartford Hospital. Connecticut State M. J. 12: 625-631, July, 1948.

Webster, H. C. [Univ. Queensland, Brisbane, Australia]: Accuracy in radon work. Brit. J. Radiol. 21: 186-188, Apr., 1948.

Weill, René: Fibrome et radium. [Fibroma and radium.] J. de méd. de Paris 68: 5-6, Jan., 1948. —Indications for use.

Wilson, C. W., & Greening, J. R. [Westminster Hosp., London, Eng.]: Gamma-ray protection in radium therapy. Brit. J. Radiol. 21: 211-220, May, 1948.

RADIOACTIVE ISOTOPES

Brues, A. M. [Argonne Nat. Lab., Chicago, Ill.]: Pathologic effects of ionizing radiations and radioactive materials. Biochem. J. 42 (1): xxii, 1948.

Lacassagne, A.: Observation chez l'homme, en conséquence de l'explosion de bombes atomiques, des principaux syndromes connus en radiophysiologie expérimentale. [Observation in man, as a result of the explosion of the atomic bomb, of the principal syndromes known in experimental radiophysiology.] Bull. Acad. nat. méd. 132 (7/8): 104-107, 1948.

MacDonald, A. M.; Cobb, Jock, & Solomon, A. K. [Harvard M. Sch., Boston, Mass.]: Radioautogram technique with C^{14}. Science 107: 550-552, May 21, 1948.

Mallet, L.; Maurin, R., & Lagourgue, M.: Traitement des nodules cancéreux par le radiophosphore en applications externes. [Treatment of cancerous nodules by externally applied radiophosphorus.] J. de radiol. et d'électrol. 28 (9/10): 424-425, 1947.—About 23,000 r were applied in the course of 10 days; 15 days later no cancer cells were found in biopsy.—*M. C. J.*

Medes, Grace [Lankenau Hosp. Res. Inst., Philadelphia, Pa.]: Isotopes in medicine. Am. J. Clin. Path. 18: 351-363, May, 1948.

Ronquès, Lucien: Le Radiophosphore en thérapeutique. [Radiophosphorus in therapeutics.] Presse méd. 56: 151-153, Feb. 28, 1948.—Radiophosphorus is very efficacious in erythremia when injected intravenously. In chronic leukemia, it does not seem superior to x-ray therapy, but might be used as an adjuvant to x-rays to maintain a near-normal leukocyte count. The results are poor in acute leukemias and Hodgkin's disease. In multiple myelomas, it exerted only temporary effect. Radiophosphorus, applied locally, penetrated only slightly and should be used only for superficial lesions. The first results are encouraging in basal-cell epitheliomas, dyskeratoses, verrucas; it was less effective in angiomas and cutaneous metastases.—*Auth. Summ.*

ANATOMICAL REGIONS

D'Errico, Giovanni [Univ. Napoli, Italy]: Voluminosissimo teratoma dello spazio retto-sacro-coccigeo, contenente un abbozzo di arto inferiore, operato con successo. [Large teratoma of the rectosacrococcygeal space, containing a deformed lower extremity, successfully operated upon.] Riforma med. 61: 467-471, Oct. 15, 1947.

NECK

Jakobsson, Elmar [St. Erik Krankenh., Stockholm, Sweden]: Über die klinische Bedeutung der Untersuchung der supraklavikulären Lymphknoten beim Krebs. [The clinical significance of the examination of supraclavicular lymph nodes in cancer.] Acta chir. Scandinav. 96: 75-86, Sept. 10, 1947.

Knezevic, Mirko [Univ. Zagreb, Yugoslavia]: Über das sogenannte cerebroma colli cysticum. [So-called cystic cerebroma of the neck.] Zentralbl. f. allg. Path. u. path. Anat. 83 (7/8): 281-285, 1947.—Case report of a

cystic teratoma of the neck that may be regarded as an intermediate stage between the usual three-layer teratomas of the neck and the so-called cerebromas.—*Auth. Summ.*

THORACIC CAVITY

Barker, Vincent L., & Caes, Henry J. [M. C., U. S. Navy]: **Ganglioneuroma. Report of a case of intrathoracic ganglioneuroma.** U. S. Nav. M. Bull. 48: 298-302, Mar./Apr., 1948.

Connolly, Earl A., & Lempka, Arnold W. [Creighton Univ. Sch. Med., Omaha, Nebr.]: **Mediastinal tumors.** Clin. Med. 55: 125-126, May, 1948.

Crandell, Walter [New York Univ. Coll. Med., New York City]: **Surgery of mediastinal tumors.** Bull. U. S. Army M. Dept. 8: 372-378, May, 1948.

Doub, Howard P. [Henry Ford Hosp., Detroit, Mich.]: **Roentgen studies of thoracic tumors.** Pennsylvania M. J. 51: 968-975, June, 1948.

Lloyd, Milton S. [New York City]: **Tumors of the anterior mediastinum. A report of six cases.** Dis. of Chest 14: 396-414, May/June, 1948.—Lipoma, lymphangioma, dermoid cyst, "undifferentiated tumor," 2 teratomas.

McIntosh, Harriet C. [New York Infirmary, New York City]: **Chest surveys and other radiologic procedures at the Strang Cancer Prevention Clinic of the New York Infirmary.** J. Am. M. Women's A. 3: 135-136, Apr., 1948.—The findings in 1342 routine chest fluoroscopies done in 1946 are presented in tabular form and discussed. There was no case of primary or metastatic cancer.—*D. A. S.*

BREAST

Ammich, O., & Günsel, E. [Marburg, Germany]: **Zur Strahlenbehandlung des Mamma-Karzinome. [Radiotherapy of breast cancer.]** Strahlentherapie 77 (1): 17-26, 1947.

Bogetti, Hugo, & Fiannaca, Plácido: Cáncer gelatinoso de la mama. [Gelatinous cancer of the breast.] Rev. Asoc. méd. argent. 61: 685-686, Sept. 15-30, 1947.—Case report.

Brown, Robert L.: Scarborough, J. Elliott, & Davis, M. Bedford [Emory Univ. Sch. Med., Ga.]: **Carcinoma of the breast.** South. Surgeon 14: 94-100, Feb., 1948.—Factors affecting treatment and prognosis of breast cancer are studied in a group of 148 cases, 49 treated more than 5 yrs. ago. The prognosis in younger women is favorable—18 (75%) of 24 women less than 40 yrs. of age are well at present, compared to 60 (48.3%) of 124 more than 40 yrs. Parity had no bearing on prognosis, for about 50% survived in each group; neither did the location of the tumor within the breast, for between 50 and 60% survived in each sector. Pain was noted in the involved breast in 25% of all cases. Clinical impression of axillary-node involvement erred in 18 (17%) of 108 cases. Local recurrence was noted in 3 (2.8%) of 106 cases treated by radical mastectomy with primary closure. With very thin skin flaps and meticulous dissection of the axilla from the apex downward, routine skin grafting need not be employed. Edema of the arm occurred in 9% of patients who received postoperative x-rays and in 4.7% of those who did not receive x-rays. 25 (51%) of 49 cases treated more than 5 yrs. ago are well. This includes 16 (80%) of 20 cases in stage I, 9 (40.9%) of 22 cases in stage II, and only 1 case (alive with cancer) of 7 in stage III.—*J. A. Urban, M. D.*

Busk, T., & Clemmesen, J. [Nat. Anti-Cancer League, Copenhagen, Den.]: **The frequencies of left- and right-sided breast cancer.** Brit. J. Cancer 1: 345-351, Dec., 1947.—Among 4139 cases of female breast cancer notified from hospitals to The Danish Cancer Registry, 2117 tumors were localized to the left and 1908 to the right breast, while 97 were bilateral and 17 without statement of side. Applying a special test, the authors demonstrated that, provided cancer frequency of the 2 breasts was the same, only 1 out of 1000 samples of the size investigated could be expected to show a deviation equal to, or exceeding, the difference observed. Smaller materials from Switzerland, 1935, and England, 1926, show similar features. Thus, for each 100 cases of cancer in the right breast, we find in Denmark 111 left-sided, and in Switzerland 113 left-sided tumors. The English material shows a higher frequency of injury to the left than to the right breast. [Of questionable significance. What is the relative frequency of nursing from each breast?—*F. W. S.*]—*Auth. Summ.*

Cade, Stanford [Westminster Hosp., London, Eng.]: **Modern treatment of carcinoma of the breast.** M. Press 219: 435-438, May 19, 1948.

Dargent, M., & Papillon, J. [Centre anticancéreux, France]: **La place actuelle de la téléroentgenthérapie dans le traitement du cancer du sein. [The place of teleroentgentherapy in the treatment of breast cancer.]** Lyon chir. 42: 585-593, Sept./Oct., 1947.—A review.

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Dawson, E. K. [Roy. Coll. Physicians, Edinburgh, Scotland]: **The genesis and spread of mammary cancer. Lecture delivered at The Royal College of Surgeons of England on 16th July, 1947.** Ann. Roy. Coll. Surgeons England 2: 241-247, May, 1948.

Di Pietro, Arturo [Inst. Municipal Radiol. y Fisioterapia, Buenos Aires, Argentina]: **Carcinosarcoma de mama. [Carcinosarcoma of the breast.]** Rev. Asoc. méd. argent. 61: 744-746, Oct. 15-30, 1947.—Case report.

Gershon-Cohen, J., & Hodes, Philip J. [Philadelphia, Pa.]: **Tumors of the breast. Preoper-**

ative roentgenography. Surg., Gynec. & Obst. 86: 723-728, June, 1948.

Giacomelli, V. & Goisis, M. [Inst. Naz. Studio e Cura dei Tumori, Milan, Italy]: Terapia associata ormonica-chirurgica-radiologica del cancro inoperabile della mammella. [Hormonal-surgical-radiologicnl treatment of inoperable cancer of the breast.] Tumori 21 (6): 338-345, 1947.

Lee, George Q. [Alexander Blain Hosp., Detroit, Mich.]: Testosterone for metastatic breast carcinoma. Alexander Blain Hosp. Bull. 7: 54-70, May, 1948.—Preliminary observations of results of treatment of 4 cases.

Magendie: Tinguud, & Labarbe: Sur un cas de mastite carcinomateuse. [A case of carcinomatous mastitis.] Bordeaux chir. [1947]: 181-184, Oct., 1947.—Epithelioma.

Meirowsky, E.: Vacuoles in Paget's disease. Exper. Med. & Surg. 6: 203-212, May/Aug., 1948.—In 4 cases of early Paget's disease, virus-like bodies were found within intranuclear vacuoles. The author believes that their presence within vacuoles, as in many virus diseases, can hardly be accidental.—*D. A. S.*

Nicolson, Wm. Perrin, Jr., & Grady, Edgar D. [Atlanta, Ga.]: Carcinoma of the breast. Ann. Surg. 127: 992-1009, May, 1948.—Analysis of 905 cases.

Perlasca, Giancarlo [Univ. Milano, Italy]: Radioterapia post-operatoria complementare del cancro della mammella. [Postoperative radiotherapy in cancer of the breast.] Tumori 21 (4/5): 213-216, 1947.

Ramseyer, M. [Lausanne, Swtz.]: Deux cas de fibrose pulmonaire due à un traitement radiothérapique d'un carcinome du sein. [Two cases of pulmonary fibrosis caused by radiotherapy of breast cancer.] Radiol. clin. 17: 53-56, Jan., 1948.

Richards, G. E. [Toronto Gen. Hosp., Ont.]: Mammary cancer. The place of surgery and of radiotherapy in its management. Part II. Radiotherapeutic procedures. Brit. J. Radiol. 21: 249-258, May, 1948.—Detailed description of irradiation technique, including 7 charts showing tumor dosage in breast and axilla with varying factors.—*D. A. S.*

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Saphir, Otto, & Amromin, George D.: Obscure axillary lymph node metastases in carcinoma of the breast. Proc. Inst. Med. Chicago 17: 140, June 15, 1948.

Sicard, André [Paris, France]: L'utilisation des hormones mâles dans le traitement du cancer du sein chez la femme. [The use of male hormones in the treatment of cancer of the female breast.] Presse méd. 56: 149, Feb. 28, 1948.—After radical mastectomy and surgical or x-ray castration, the author uses 10 injections of 100 mg. testosterone every 3 mos.—*M. C. J.*

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Toone, W. M.: Treatment of carcinoma of the breast with testosterone therapy. Bull. Vancouver. M. A. 24: 118-119, Jan., 1948.

Waltman, Charles A. [Easton Hosp., Easton, Pa.]: The treatment of advanced cancer of the female breast with testosterone propionate. Staff Bull. Easton Hosp. 1: 11-22, June, 1948.—Report of 7 cases.

Warren, Shields [Harvard M. Sch., Boston, Mass.]: Tumor Seminar. [A] Intraductal papilloma of the breast. [B] Cystosarcoma of the breast. J. Missouri State M. A. 45: 366-368; 368-373, May, 1948.

Watrin: Michon, F., & Guervain: Néoplasme du sein présentant cliniquement comme une maladie de Paget. [Neoplasm of the breast which appeared clinically to be Paget's disease.] Rev. méd. Nancy 72: 386-387, Dec. 1/15, 1947.—The case was finally diagnosed as cancer of the breast in an aberrant, subareolar section of mammary gland.—*M. C. J.*

Wolffson, Sol M. [Cook Co. Hosp., Chicago, Ill.]: Choosing the therapy for the breast cancer patient. Illinois M. J. 93: 322-326, 1948.

CARDIOVASCULAR SYSTEM

Braun, Winston, & Hoffmann, George Towle [M. C., U. S. Navy]: Metastatic tumor in the heart. Report of a case. U. S. Nav. M. Bull. 48: 275-277, Mar./Apr., 1948.—Primary carcinoma of liver with myocardial metastases.

Brindley, G. V., & Brindley, G. V., Jr. [Scott & White Hosp., Temple, Tex.]: Lymphangioma

of the mesentery. Ann. Surg. 127: 907-911, May, 1948.—Case report.

Chamberlain, Richard H., & Pendergrass, Eugene P. [Hosp. Univ. Pennsylvania, Philadelphia]: **Some considerations regarding the treatment of hemangiomas.** Pennsylvania M. J. 51: 867-869, May, 1948.

Crawford, G. Marshall [Massachusetts Gen. Hosp., Boston]: **Injection therapy for angiomas.** J. A. M. A. 137: 519-527, June 5, 1948.

Ewing, M. R.: Large angio-endothelioma of buttock. Brit. J. Surg. 35: 436-438, Apr., 1948.—Case report.

Goeringer, C. Fred [Hosp. Univ. Pennsylvania, Philadelphia]: **Hemangiomas of striated muscle.** Am. J. Surg. 76: 58-65, July, 1948.—Review of the literature and 3 case reports.

Holland, Daniel J. [Brookline, Mass.]: **Hemangioma of the cheek.** J. Oral Surg. 6: 167-168, Apr., 1948.

Janes, J. M., & Ghormley, Ralph K. [Mayo Clin., Rochester, Minn.]: **Hemangio-endothelioma treated with radiophosphorus and roentgen rays.** Proc. Staff Meet., Mayo Clin. 23: 235-238, May 12, 1948.—Report of 2 cases.

McCoy, James J. [M. C., U. S. Navy]: **Hodgkin's disease involving the epicardium.** U. S. Nav. M. Bull. 48: 272-275, Mar./Apr., 1948.

Pearson, J. E. G. [Mt. Vernon Hosp., London, Eng.]: **Myocardial metastasis by bronchial carcinoma and other neoplasms.** Brit. J. Tuberc. 42: 31-38, Apr., 1948.—Report of 20 cases and review of the literature.

Rabson, S. M., & Thill, L. J. [St. Joseph Hosp., Fort Wayne, Ind.]: **Epithelium-like inclusions in the heart.** Am. J. Path. 24: 655-661, May, 1948.—Coincidental autopsy findings in a 29-yr.-old white woman who died of rheumatic fever were multiple small lesions in the posterior leaflet of the mitral valve, adjacent left atrium, and ventricle, in the general plane of the valvular ring. These were generally round, solid, and hollow, with no evidence of a physical bridge between the structures and the endocardium or epicardium. Microscopically they were formed of generally polyhedral or cuboidal cells peripherally, while the center of the structures showed hollowing accomplished by disintegration of the cells, leaving degenerating cells and cellular detritus. Some of the early stages of luminal formation lent the appearance of sebaceous glands. Somewhat similar lesions in the heart have previously been reported, having variously been termed "primary epithelial tumor," "lymphangio-endothelioma," and "congenital epidermoid cyst." Histogenetic speculations have considered ectodermal heterotopia, metaplasia of retained entodermal cells, "lymphatic vasoformation," inclusion of pericardial elements in the atrial wall, metaplasia of an epicardial anlage and a common origin with the bronchial wall. In the present case endocardial or epicardial origin with dystopia, heterotopia, or inclusion seemed reasonable, in the absence of definite identification of the abnormal formations as epithelial.—*A. G. Foraker, M. D.*

Reich, William W., & Van Tassell, Lloyd R. [Berkeley, Calif.]: **Cystic hemangioma of the spleen.** Am. J. Surg. 75: 840-844, June, 1948.—Case report.

Sorrell, E., & Dujardin, A.: A propos d'une tumeur glomique de l'espace interdigital. [A glomus tumor of the interdigital space.] Rev. d'orthop. 33: 457-467, Oct./Dec., 1947.

Stewart, Fred W., & Treves, Norman [Memorial Hosp., New York City]: **Lymphangiosarcoma in postmastectomy lymphedema. A report of six cases in elephantiasis chirurgica.** Cancer 1: 64-81, May, 1948.

Warren, Shields [Harvard M. Sch., Boston, Mass.]: **Tumor Seminar. Hemangiopericytoma of retroperitoneal space.** J. Missouri State M. A. 45: 380-382, May, 1948.

DIGESTIVE TRACT

Borges, E. J. [Tata Memorial Hosp., Bombay, India]: **The early diagnosis and treatment of cancer of the alimentary tract.** Indian J. M. Sc. 2: 223-232, Apr., 1948.

ORAL CAVITY

Anon. [New York Inst. Clin. Oral Path., New York City]: **Case reports: Fibroma of the cheek. A fibroma of the palate. Pregnancy tumor.** New York State Dent. J. 14: 257-258; 258-259; 259-261, May, 1948.—Three intraoral lesions; 1, an angiogranuloma.

Bonrgoyne, Julious R. [Memphis, Tenn.]: **Surgery of the mouth and jaws. Chapter XXI. Cysts of the jaws.** Dental Items of Interest 70: 35-51, Jan.; 126-139, Feb.; 251-263, Mar., 1948.

Boyko, G. Victor [Paterson, N. J.]: **Classification of extensive cysts of the jaws.** J. Oral Surg. 5: 325-336, Oct., 1947.

Cameron, Charles S. [Am. Cancer Soc., New York City]: **The possible etiology of mouth cancer.** New York State Dent. J. 14: 232-242, May, 1948.

Clark, Henry B., Jr. [St. Paul, Minn.]: **Removal of massive scar tissue growth and benign polyp caused by ill-fitting lower denture.** J. Oral Surg. 5: 348-350, Oct., 1947.

Hickey, Maurice J. [Columbia Univ., Sch. Dent. & Oral Surg., New York City]: **The diagnosis of oral cancer.** New England Dent. J. 1: 15-17, Jan., 1948.

Humphreys, H. F. [Univ. Birmingham, Eng.]: **A note concerning carcinoma of the gum.** Dental Rec. 68: 104, Apr., 1948.

Jorstad, Louis H. [Barnard Free Skin & Cancer Hosp., St. Louis, Mo.]: **Diagnosis and treat-**

ment of carcinoma of buccal mucosa. Mississippi Valley M. J. 70: 45-46, Mar., 1948.

Lloyd, Ralph S. [Baltimore Marine Hosp., Md.]: Role of the dentist in oral cancer detection. Pub. Health Rep. 63: 805-812, June 18, 1948.

Maitland, G. R. [Detroit, Mich.]: Atypical adamantinoma of the maxilla: report of case. J. Oral Surg. 5: 351-355, Oct., 1947

Moore, Paul A. [Nat. Naval M. Center, Bethesda, Md.]: Clinical diagnosis of neoplasms of the oral cavity. Suggestions on procedural routine. Oral Surg., Oral Med. & Oral Path. 1: 488-491, May, 1948.

Oliveira, Luiz Carlos, de: Câncer da lingua. [Cancer of the tongue.] Hospital, Rio de Janeiro 33: 257-272, Feb., 1948.—A review.

Sealey, Vernon T. [Univ. Melbourne Dent. Sch., Australia]: An unusual tumour on the palate. Australian J. Dent. 52: 177-178, May, 1948.—Case report: myxofibroma.

Sharp, George S. [Los Angeles, Calif.]: California Cancer Commission Studies. Chapter XII. Cancer of the oral cavity. California Med. 68: 457-464, June, 1948.

Smith, James B. [Danville, Pa.]: Cancer of the floor of the mouth. J. Oral Surg. 6: 106-115, Apr., 1948.—General discussion and case report.

SALIVARY GLANDS

Bailey, Warwick H. [War Memorial Hosp., Scunthorpe, Eng.]: A case of mixed salivary gland tumour arising from ectopic tissue. Brit. J. Surg. 35: 431-432, Apr., 1948.

Clausen, Edwin G., & Henley, R. Bruce [Univ. California M. Sch., San Francisco]: The surgical treatment of mixed tumors of the parotid gland. California Med. 68: 366-369, May, 1948.

Pricolo, V., & Colozza, G. [Inst. Naz. Studio e Cura dei Tumori, Milan, Italy]: Gli epiteliomi della ghiandola sottomascellare (considerazioni anatomopatologiche, cliniche e terapeutiche). [Epithelioma of the submaxillary gland (anatomico-pathological, clinical and therapeutic considerations.] Tumori 21 (6): 285-296, 1947.—A report of 10 cases.

Fayata, Benedict V. [Univ. Rochester Sch. Med. & Dentistry, New York]: Characteristics of mixed tumors of the parotid gland growing in vitro. Surg., Gynec. & Obst. 86: 659-662, June, 1948.—Material from 5 histologically similar mixed tumors of the parotid gland showed similar cultural characteristics when grown in vitro. Histologically these neoplasms were composed of clumps of small epithelial cells, some forming acini, lying in masses of matrix resembling cartilage. During the 1st wk. only a few small macrophages migrated from the explants, followed by fibroblasts. In the 3d wk. epithelial elements appeared, later growing in broad sheets with an evenly spaced mosaic pattern, forming cords and acini at the growing edges. Later the large epithelial sheets developed focal areas of small acidophilic cells with gradual vacuolization, disappearance of cells, and space formation. Most of the cultures died within 140 days with regressive changes dominant in the last 6 wks. Tissue from the parotid gland of a 4-mo.-old human fetus contained only ducts and no recognizable acinar components, which develop in the 5th mo. of uterine life. Explants from this tissue, grown in vitro, resembled closely those of the cultures made from mixed tumors, although embryonal cells grew less vigorously.

The study suggests that mixed tumors may be derived from cells lining the ducts of salivary glands and that the characteristic pleomorphism may result from secondary changes in a neoplasm composed almost exclusively of epithelium. The culture is bathed in a fluid that may remove the products of cell disintegration, but the growing tumor with its relatively poor blood supply to its interior must store these products as a gel which contains some viable-appearing cells. The end result would approximate closely the appearance of cartilage or myxomatous tissue. While these observations support those who adhere to the epithelial nature of mixed tumors, they do not form any basis for discriminating between the embryonal or adult nature of the cell of origin. However, as cancer research progresses, the argument that misplaced embryonal cells give rise to neoplasms becomes progressively more tenuous.—*A. G. Foraker, M.D.*

McKechnie, R. E. [Vancouver M. Clin., B. C.]: A large parotid tumor causing pharyngeal obstruction. Bull. Vancouver M. A. 24: 249-251, Apr., 1948.—Case report: mixed tumor weighing 206 gm.

Taylor, Grantley W., & Garceau, Gerald G. [Massachusetts Gen. Hosp., Boston]: Tumors of salivary-gland origin. New England J. Med. 238: 766-768, May 27, 1948.—The tumors of the salivary glands seen at the Massachusetts General Hospital from 1930 to 1941 and at the Pondville State [Cancer] Hospital from 1927 to 1941 are reviewed. There were 115 mixed tumors and 61 cancers of the parotid, 16 mixed tumors and 12 cancers of the submaxillary salivary gland, and 12 and 2 respectively of the accessory salivary glands. The high ratio of cancers is explained by the inclusion of the Pondville cases. The relatively high percentage of cancers in the submaxillary salivary-gland tumors is again emphasized in this series. Cancer was found in 16% of the mixed tumors. If an ill-defined and hard tumor of the parotid had a history of less than 1 yr. in a patient in the 6th decade, it was most often cancer. This was especially true if there was tumor fixation, associated facial-nerve paralysis, and abnormally palpable regional lymph nodes. 47% of the cancers of the parotid metastasized to nodes; about 25% had distant metastases, especially to the lung, liver, and bones. The cancer cases were usually diagnosed late and often at the time of surgery.

In the mixed tumors, best results were ob-

tained by wide surgical extirpation of the tumor and the contiguous, uninvolved parotid salivary gland with visualization of the facial nerve early in the operation. Recurrences and facial-nerve injury were more common after simple enucleation of the tumor. There were more recurrences following surgery on the larger tumors—which the authors believe is contrary to McFarland's findings. Recurrences developed in 25% of the cases in which the tumor capsule was ruptured. One-half of all recurrences developed after 5 yrs. This frequency of local recurrences after surgery, often leading to mortality without evidence of metastases, indicates the need for very extensive local excision in cancer of the parotid. The facial nerve is sacrificed readily, if indicated. An elective radical neck dissection is combined with local surgery. Cancer of the submaxillary salivary gland is similarly treated. The authors feel radiation therapy is probably of no value as a primary or adjunct modality.

The end results are not analyzed on the basis of any specific statistical method. Of 61 cases of parotid cancer, 33 were operated on with 5 "cures." There were no cures in 17 cases treated by radiation alone. There were 19 recurrences in the operative field. Of 12 cases of cancer of the submaxillary salivary gland, 10 were operated on with no cures—because of failure to control the primary disease and not because of metastases.—*S. L. Perzik, M.D.*

ESOPHAGUS

Amesti, Felix, de, & Otaiza, Eliseo [Univ. Chile, Santiago]: Cardioesophageal cancers treated via the transthoracic and transdiaphragmatic route. Surgery 23: 921-934, June, 1948.—Analysis of 39 cases: 35.89% resectability; 15.38% (of total) survival; average survival 13 mos.—*D. A. S.*

Cooper, Donald R., & Buxton, Robert W. [Univ. Michigan, Ann Arbor]: Gastrostomy. A statistical review of one hundred ninety-nine cases. Surgery 23: 821-831, May, 1948.

Decker, P. [Lausanne, Swtz.]: Chirurgie du tube digestif par voie transpleurale. [Transpleural surgery of the esophagus.] Helvet. chir. acta 14: 364-369, Oct., 1947.

Kenworthy, Roger A., & Welch, C. Stuart [Tufts Coll. M. Sch., Boston, Mass.]: Leiomyoma of the esophagus and cardia of the stomach. Surgery 23: 745-752, May, 1948.—Case report and review of the literature.

Kinsella, Thomas J. [Minneapolis, Minn.]: Carcinoma of the esophagus. Resection, high esophagogastrostomy. Minnesota Med. 31: 679-682, June, 1948.—Case report.

Lefevre, Lucien: Le traitement radiothérapique du cancer de l'oesophage. [Radiotherapy of esophageal cancer.] Paris méd. 38: 142-146, Mar. 20, 1948.

Maier, Herbert C. [New York City]: Preoperative, operative, and postoperative care in esophageal resections. Surgery 23: 884-892, June, 1948.

Mason, James M., III [Birmingham, Ala.]: The surgical treatment of obstructive lesions of the esophagus. Ann. Surg. 127: 1067-1078, May, 1948.

Monchet, Alain: Traitement chirurgical du cancer de l'oesophage thoracique. [Surgical treatment of cancer of the thoracic esophagus.] Paris méd. 38: 137-142, Mar. 20, 1948.—A review.

Nagel, Gunther W. [Stanford Univ. M. Sch., San Francisco, Calif.]: Lesions of the esophagus: diverticulum, cardiospasm, megaesophagus and cancer. M. Clin. North America [1948]: 363-372, Mar., 1948.

Olivier, Cl. [Clin. chir. Salpêtrière, Paris, France:] Place de la tunnelisation cervico-abdominale dans le traitement du cancer de l'oesophage. [The place of the cervico-abdominal tunnel in treatment of esophageal cancer.] Presse méd. 56: 2, Jan. 3, 1948.—Discussion of operative technique.

Pack, George T. [New York City]: Introduction to symposium on cancer of the esophagus and gastric cardia. Surgery 23: 867-873, June, 1948.

Rudler: Cancer du cardio-oesophage enlevé par voie thoracique gauche. Guérison opératoire. [Cancer of the cardial end of the esophagus, removed by the left thoracic approach. Operative cure.] Mém. Acad. de chir. 73 (33/34): 691-692, 1947.

Stephens, H. Brodie [San Francisco, Calif.]: California Cancer Commission Studies. Chapter XVII. Carcinoma of the esophagus. California Med. 68: 388-391, May, 1948.—Brief general discussion.

Strieder, John W. [Boston City Hosp., Mass.]: Surgical management of carcinoma of the lower two-thirds of the esophagus and cardiac end of the stomach. J. Thoracic Surg. 17: 143-161, Apr., 1948.—From 1941 to 1947, 71 patients with carcinoma of the esophagus and cardial end of the stomach were operated upon, of whom 46 had resectable lesions. Preoperative preparation included dental prophylaxis, transfusions for anemia, adequate parenteral fluids with amino acids to improve the blood-protein level, administration of 50,000 units of penicillin every 3 hrs. for 2 days prior to surgery, lavage of the esophagus with half-strength Dakin's solution twice daily when there was complete or nearly complete esophageal obstruction, and, when necessary, preliminary jejunostomy to improve the patient's nutritional status. The anesthesia and operative techniques are reported in detail.

The thoracicoabdominal approach was not used in this series. The cases were considered inoperable only when there was invasion of vital structures which could not be removed with the tumor. Palliative resections were done if the pri-

mary growth was resectable, even though distant metastases were apparent at operation. Complications included leak at the site of esophagogastric anastomosis, pulmonary atelectasis, and occasional late strictures. The technical difficulties and poorer results obtained when it was necessary to perform the anastomosis above the arch of the aorta are stressed. There was an over-all operative mortality for resected cases of 38.2%. When the anastomosis could be done below the arch of the aorta (35 cases), the mortality was 24%; when it was necessary to do the anastomosis above the arch (12 cases), 63.6%. The resection mortality for the period 1945-1947 was but 12% for anastomosis below the arch and 55.5% above the arch, a marked improvement. Of 26 operative survivors in the latter period, 1945-1947, 21 are still alive from 1 to 14 mos. later.—*L. W. Guiss, M. D.*

STOMACH

Armstrong, Charles D., & Willmr, Dwight L. [Stanford Univ. M. Sch., San Francisco, Calif.]: Malignant disease of the stomach simulating gastric diverticulum. M. Clin. North America [1948]: 336-354, Mar., 1948.—Discussion and 2 case reports: lymphosarcoma and adenocarcinoma.

Bell, H. Glenn [San Francisco, Calif.]: California Cancer Commission Studies. Chapter XIX. Carcinoma of the stomach. California Med. 69: 74-76, July, 1948.

Block, Malcolm: Griep, Arthur H., & Pollard, H. Marvin [Univ. Michigan Hosp., Ann Arbor]: The occurrence of gastric neoplasms in youth. Am. J. M. Sc. 215: 398-404, Apr., 1948.

Burlando, Adolfo J.: Diagnóstico radiológico precoz del cáncer gástrico. Resumen del relato oficial ante el segundo congreso interamericano de radiologia. [Early radiological diagnosis of gastric cancer. Résumé of the official report before the second interamerican congress on radiology.] Rev. san. mil. argent. 46: 563-567, Oct./Dec., 1947.

Cohn, Allan L., & Gold, Rubin L. [Mt. Zion Hosp., San Francisco, Calif.]: Prepyloric spasm simulating gastric malignancy. Gastroenterology 10: 782-791, May, 1948.—Eight case reports.

Cook, Albert W. [Brooklyn Hosp., New York City]: Factors favoring and hindering early diagnosis of carcinoma of the stomach. An analysis of 117 cases. Brooklyn Hosp. J. 6: 67-73, Apr., 1948.

Crismer, Roger [Univ. Liége, Belg.]: Le diagnostic radioclinique du cancer du pôle supérieur de l'estomac et en particulier du cancer juxtacardiaque. [Radiological diagnosis of cancer of the superior pole of the stomach, particularly juxtacardial cancer.] Acta gastro-enterol. belg. 11: 84-93, Feb., 1948.—A discussion of diagnostic problems and 5 case reports.

Crousse, R., & De Witte, J. [Brussels, Belg.]: Sarcomes primitifs de l'estomac. [Primary sarcomas of the stomach.] Acta gastro-enterol. belg. 11: 23-34, Jan., 1948.—Two case reports.

Cubides, Hernando Anzola [Bogotá, Colombia]: A propósito de la gastrectomía total. [Total gastrectomy.] J. Internat. Coll. Surgeons 11: 223-224, Mar./Apr., 1948.

De Busscher, Georges [Univ. Ghent, Belg.]: La vascularisation macroscopique et microscopique du cancer de l'estomac. [Macroscopic and microscopic vascularization in gastric cancer.] Acta gastro-enterol. belg. 10: 481-488, Nov./Dec., 1947.—X-rays of injected stomachs and microscopic studies—*M.C.J.*

Finkelstein, Ch. [Roten-Kreuz-Krankenh., Kaunas, Lithuania]: Zur Frage der Behandlung des inoperablen Magenkrebses mit Autovaccinationen von Magensaft des Kranken. [Treatment of inoperable gastric carcinoma by autovaccination of gastric juice.] Gastroenterologia 73 (1/2): 45-55, 1948.—Twenty patients with inoperable gastric cancer were injected with their gastric juice in a series of 20 injections, doses increasing by 0.1 cc., beginning with 0.1 cc., ending with 2.0 cc. Injections were given 2 to 3 times a week. Life was lengthened, general condition improved, and pain notably decreased (sometimes to abandonment of narcotics). War prevented adequate continuance of treatments. The possible theoretical immunological bases of the treatment are discussed.—*M. C. J.*

Freeman, G. C. [The Clinic, Honolulu, Hawaii]: Cavernous hemangioma of the stomach. Report of a case. Proc. Staff Meet. Clin., Honolulu 14: 17-20, Apr., 1948.

Guthkelch, A. N. [Manchester Roy. Infirmary, Eng.]: Endothelioma of the stomach causing acute retention of urine. Brit. J. Surg. 35: 439-440, Apr., 1948.—Case report.

Ikle, A. [Chir. Klin. Kantonsspit., St. Gallen, Switz.]: Beitrag zur Klinik und Pathologie der papillären Schleimhautgeschwülste des Magens (Magenpapillome). [Diagnosis, treatment, and pathology of papillary mucosal tumors of the stomach (gastric papillomas).] Helvet. chir. acta 14: 435-461, Dec., 1947.—Based on 7 observed cases, the clinical picture, radiological diagnosis, and pathological anatomy of adenomatous papillomas of the stomach are described. The relationship to specific types of anemia, the analogy to similar villous papillomas of the large intestine and urinary bladder, and the different pathogenetic theories are briefly considered. In spite of their initial benign appearance, the new growths must practically always be regarded as early diagnosed carcinomas. Therapeutically, therefore, gastric resection is to be preferred to any local extirpation of the tumors after the lumen of the stomach has been entered.—From *Auth. Summ.*

Kinsella, V. J. [Sydney, Australia]: Diagnosis of gastric disease: Should radiology of the stomach be abandoned? M. J. Australia 1: 609-614, May 15, 1948.

Lambling, A.: Le cancer de l'estomac. Les aspects cliniques—les images radiologiques de début—la fréquence relative des différentes formes cliniques. [Cancer of the stomach. Clinical aspects; early x-ray appearance; relative frequency of various clinical types.] Hôpital 35: 233-236, Nov., 1947.—A review.

Lorange, Margrethe [Oslo, Norway]: **Cancer ventriculi-statistikk. [Statistics on cancer of the stomach.]** Nord. med. 37: 171-172, Jan. 23, 1948.—From Jan. 1, 1919, to July 1, 1946, 707 patients with gastric cancer were treated in Vestfold County Hospital. 355 patients were operated on, a gastric resection being performed in 212. The primary operative mortality after the resection was 14.2%. Included among the above are all those who died in the hospital. 55, or 32.9%, survived more than 3 yrs.; 34, or 24.1%, more than 5 yrs. If the figures for primary operative mortality are excluded, the last two rates become 39% and 29.6% respectively.—*Auth Summ.*

Mailer, Robert [Victoria Infirmary, Glasgow, Scotland]: **Carcinoma in a thoracic stomach (congenital short oesophagus).** Brit. J. Surg. 35: 426-428, Apr., 1948.—Case report.

Marshall, Samuel F. [Lahey Clin., Boston, Mass.]: **Gastric carcinoma.** Pennsylvania M. J. 51: 841-847, May, 1948.

Orban, F., & Dalem, J. [Univ. Liége, Belg.]: **Traitement actuel des tumeurs du cardia. [Treatment of cancer of the cardia.]** Acta gastro-enterol. belg. 11: 94-100, Feb., 1948.—Three case reports.

Pack, George T., & McNeer, Gordon [Memorial Hosp., New York City]: **Surgical treatment of cancers of the gastric cardia.** Surgery 23: 976-1019, June, 1948.—Numerous factors concerning cancers involving the proximal gastric segment are presented. *Incidence:* 16% of gastric carcinomas involve the distal esophagus and cardia, of which 122 have been resected on the Gastric Service at Memorial Hospital by total or subtotal gastrectomy. *Diagnosis:* The main differential lies between benign cardiospasm and carcinoma. When dysphagia occurs in elderly subjects for the first time, the cause must be attributed to carcinoma until proved otherwise. Esophagoscopy is invariably indicated after adequate radiographic study. *Operative Technique:* The evolution of the operation of transthoracic esophagogastrectomy is thoroughly studied. The technique of the operation as presently performed is described and illustrated by artists' drawings. *Pre- and Postoperative Care:* Meticulous attention to the innumerable minutiae is required for successful management. Restoration to normal blood status prior to operative intervention is advised. The routine use of tracheal suction is responsible for decreased pulmonary complications. Nutritional management in the postoperative phase is discussed. *Complications* tend to be more frequent than in other gastric operations. They are mainly pulmonary and cardiovascular. Fistula and stenosis occur less frequently since adoption of interrupted silk technique. *Resectability Rate:* 59.5%. *Operative Mortality:* 33%. *End Results:* 2 patients survived resection of cardia for 5 yrs. without recurrence. These operations were done with such infrequency prior to 1942 that adequate estimates of 5-yr. survival rates are worthless at this time.— *G. P. McNeer, M. D.*

Pack, George T., & McNeer, Gordon [Memorial Hosp., New York City]: **The incidence of gastric cancer.** Internat. Abstr. Surg. 86: 521-534, June, 1948.—The incidence of gastric cancer has been reported in such divergent ways that accurate data are obtained with difficulty. For many years the disease was included with cancer of the liver in all statistical analyses without taking into account the numerous neoplasms which metastasize to the liver. Again, the accurate reporting of cancer of the stomach depends on expert radiographic and surgical interpretation. All too often a doctor, called to a dying patient, has palpated the abdomen and finding a mass in the epigastrium, certified the cause of death as gastric cancer. *Age and Sex:* Cancer is not, for the most part, a reportable disease; hence, in attempting to evaluate the true incidence of gastric carcinoma, the most reliable indices remain mortality records and institutional reports. In 1940, 26,135 persons were known to die of this disease; 61.6% were males and 38.4%, females. It is primarily a disease of middle and later life, occurring most frequently between the 50th and 70th yrs., only 10.1% occurring before the 6th decade, and 0.6% before the age of 30. *Race:* Comprehensive data on the racial incidence of gastric cancer are unobtainable. In 1940, the Negro death rate in the United States from gastric cancer was reported as 14.4 per 100,000 as compared to 20.4 for the white population. If anything, the disease was shown to be slightly more prevalent among non-Jews than Jews in Budapest, Amsterdam, and Berlin. In East Sumatra cancer of the stomach occurred with far greater frequency among Chinese than Javanese coolies, both of whom lived under identical conditions. A study of the geographical distribution of gastric cancer throughout the world as compared to various sections of the United States brought to light several interesting factors which undoubtedly bear a direct relationship to the reported incidence. The statistical data are affected by: the percentage of the population of any geographical area which arrives at or above the age of 50, the available facilities for medical care, and the economic status of a country—hence the supposed infrequency of the disease in the Middle East, India, and the deep South states. The extraordinarily high incidence of gastric cancer in Germany and the Scandinavian countries is noted. Of all the organs of digestion, the stomach is the most vulnerable to the occurrence of cancer.—*G. P. McNeer, M. D.*

Payne, John H., & Clagett, O. Theron [Mayo Clin., Rochester, Minn.]: **Transthoracic gastric resection for lesions of cardia of stomach and lower part of esophagus.** Review of

cases. Surgery 23: 912-920, June, 1948.—Analysis of 33 cases: 13% operative mortality; 71% 1-yr., 40% 2-yr., and 31% 3-yr. survivals. —*D. A. S.*

Poinot, M. J.: Deux cas de cancers perforés de l'estomac. [Two cases of perforating cancer of the stomach.] Bordeaux chir. [1947]: 184-185, Oct., 1947.

Priestley, James T., & Kumpuris, Frank [Mayo Clin., Rochester, Minn.]: Total gastrectomy with esophagoduodenal anastomosis. Arch. Surg. 56: 145-152, Feb., 1948.—Discussion and description of technique of esophagoduodenostomy, with report of 2 cases: gastric ulcer and gastric carcinoma.

Ramseyer, Marc [Cantonal Hosp., Lausanne, Swtz.]: Récidive pédiculé d'un carcinome de l'estomac dont la tumeur primitive, déjà pédiculée, fut excisée. [Pedunculated recurrence of a carcinoma of the stomach in which the primary tumor, also pedunculated, had been excised.] Radiol. clin. 17: 32-34, Jan., 1948.

Sherman, Robert S. [Memorial Hosp., New York City]: The roentgen diagnosis of cancer of the cardiac region of the stomach. Surgery 23: 874-883, June, 1948.—In x-ray study of the stomach, distinction should be made between the *detection* of an abnormality and its subsequent *diagnosis*. The detection of any organic abnormality of macroscopic size is the responsibility of the roentgenologist, along with an attempt to state whether or not the process falls in a surgical category. In x-ray study of the cardia, the particular anatomical features of the area must be well known as well as those technical features that can be utilized to advantage. The films to be taken are individualized, with some emphasis on the upright studies in the sagittal and lateral positions.

In 205 resected carcinomas of the stomach at Memorial Hospital, 22% were in the cardial region. 25 of the most recent were selected for this study, emphasis being placed upon the diagnosis of the early lesion. The basic elements of x-ray diagnosis for tumors were: the presence of ulcer, mass, and infiltrate. In these cases ulceration played a minor role. A mass was seen within the air bubble in most. Infiltrate was present in all. Involvement of the lower esophagus occurred in all but 4, but actual obstruction was infrequent. A brief discussion of the x-ray findings in the postoperative stomach following cardiectomy and esophagogastric anastomosis has been included.—*Auth. Abstr.*

Sherman, Robert S. [Memorial Hosp., New York City]: Roentgenoscopic survey for asymptomatic gastric cancer. J. Am. M. Women's A. 3: 136-138, Apr., 1948.—A preliminary statement based upon an x-ray survey of 1576 patients 45 yrs. of age or older for the detection of symptomless tumors of the stomach. The technique is described. 1399 satisfactory examinations were made; 3 tumors were discovered: myosarcoma of the lower esophagus, gastric carcinoma, gastric polyp.—*D. A. S.*

Warren, Shields [Harvard M. Sch., Boston, Mass.]: Tumor Seminar. Leiomyoma of the stomach. J. Missouri State M. A. 45: 360-364, May, 1948.

Watrin; Girard, J., & Vichard, G.: Un cas d'acanthosis nigricans au cours de l'évolution d'un néoplasme latent du cardia. [Acanthosis nigricans in the course of the development of a latent neoplasm of the gastric cardia.] Rev. méd. Nancy 72: 389, Dec. 1/15, 1947.—Case report.

Welch, Claude E., & Allen, Arthur W. [Harvard M. Sch., & Mass. Gen. Hosp., Boston, Mass.]: Carcinoma of the stomach. New England J. Med. 238: 583-589, Apr. 22, 1948.—In 457 cases of carcinoma of the stomach at Massachusetts General Hospital for the 10 yrs., 1937 to 1946, the average delay from onset of symptoms to hospital admission was 5 mos., essentially the same as for the previous decade. Immediate surgery is recommended in gastric-ulcer cases if the ulcer: is of short duration and the patient is more than 50 yrs. old; is more than 2.5 cm. in diameter; is on the greater curvature or in the prepyloric region; is chronic or recurrent and on the lesser curvature; if there is no free gastric HCl. There was an operability rate of 75% and a resectability rate of 50%. By the abdominal approach, the operative mortality was 3% for subtotal and 32% for total resection; by the transthoracic approach, 4% and 28% respectively. Of their resected cases, only 5% with metastatic nodes survived 5 yrs., compared with 50% of those without.—*L. W. Guiss, M. D.*

SMALL INTESTINE

Allison, T. D., & Babcock, J. R. [George F. Geisinger Memorial Hosp., Danville, Pa.]: Lipoma of the duodenum causing melena. Ann. Surg. 127: 754-756, Apr., 1948.—Case report.

Lawler, Richard H.: Tumors of the small intestine. Proc. Inst. Med. Chicago 17: 93, Apr. 15, 1948.

Lorber, Stanley H., & Machella, Thomas E. [Hosp. Univ. Pennsylvania, Philadelphia]: Enteric cyst of the duodenum. Report of a case and review of the literature. Gastroenterology 10: 892-899, May, 1948.

Mendl, K., & Tanner, C. H. [Swansea Gen. & Eye Hosp., Swansea, Wales]: Carcinoma of the duodenum. Brit. J. Radiol. 21: 309-310, June, 1948.—Case report.

Peple, W. Lowndes [St. Luke's Hosp., Richmond, Va.]: Enterogenous cysts of the duodenum. Report of a case that is unusual if not unique. Ann. Surg. 127: 912-917, May, 1948.

Ricard, A., & Franeillon, J.: Cancer de la première portion du duodénum [Cancer of the first portion of the duodenum.] Lyon chir. 42: 596-598, Sept./Oct., 1947.—Case report.

Root, J. C. [Cleveland Clin., Ohio]: Roentgenologic diagnosis of tumors of the small in-

testine. M. Clin. North America [1948]: 436-442, Mar., 1948.

Warren, Shields [Harvard M. Sch., Boston, Mass.]: Tumor Seminar. Leiomyosarcoma of the ileum. J. Missouri State M. A. 45: 364, May, 1948.

Wilensky, Abraham O. [New York City]: Tumors arising in Brunner's glands. Am. J. Digest. Dis. 15: 206-209, June, 1948.—Review of the literature.

APPENDIX

Brewer, A. Clifford, & Marcus, R. [Liverpool, Eng.]: Adenomatous appendicular polyp causing intussusception. Brit. J. Surg. 35: 434, Apr., 1948.

Clarke, Roger G.: Polyps and adenocarcinoma of the appendix. Proc. Inst. Med. Chicago 17: 140, June 15, 1948.

Crousse; Stoupel; Thiebaut, & Vandiest, L.: Les carcinoïdes de l'appendice. [Carcinoids of the appendix.] Acta gastro-enterol. belg. 11: 35-48, Jan., 1948.—A review of the literature and 5 case reports.

Dumont, R. [Hôp. civil d'Ixelles, Belg.]: Présentation d'un cas de mucocèle appendiculaire. [A case of mucocele of the appendix.] Acta gastro-enterol. belg. 11: 156-159, Mar., 1948.

COLON

Aitken, L. H., & Brown, D. B.: Multiple papillary adenomata of the intestine. New Zealand M. J. 47: 139-142, Apr., 1948.

Bacon, Harry E. [Temple Univ. Hosp. & Sch. Med., Philadelphia, Pa.], & Rowe, Robert J.: Surgery of the lower bowel. J. A. M. A. 136: 975-979, Apr. 10, 1948.

Edwards, Monte [Baltimore, Md.]: Four metachronous malignant lesions of the colon. An unusual case. Surgery 23: 808-813, May, 1948. —Four adenocarcinomas of the rectum and colon occurring over a 19-yr. period with no demonstrable polyposis: carcinoma of sigmoid colon removed May 5, 1927; carcinoma of transverse colon, June 20, 1935; carcinoma of rectosigmoid, August 5, 1941; carcinoma of transverse colon (possibly a recurrence), March 15, 1946. The patient, at present 79, has outlived 2 of his surgeons.—*D. A. S.*

Estes, William L., Jr. [Bethlehem, Pa.]: Familial polyposis and carcinoma of the colon. Ann. Surg. 127: 1035-1045, May, 1948.—Report of a family in which the mother and all 6 adult children had either multiple polyposis of the colon or carcinoma of the sigmoid or rectum, or both.—*From Auth. Summ.*

Fretheim, Bjarne: Cancer of the colon. A survey of the material for the years 1931-1946. Acta chir. Scandinav. 96 (4): 345-360, 1948.

Hughes, C. Robert, & O'Malley, Emmett J. [Cleveland Clin., Ohio]: Roentgenologic diagnosis of tumors of the large intestine. M. Clin. North America [1948]: 428-435, Mar., 1948.

Judd, Edward S., Jr. [Mayo Clin., Rochester, Minn.]: Resection for lesions of the right portion of the colon. Proc. Staff Meet., Mayo Clin. 23: 225-229, May 12, 1948.

Judd, Edward S., Jr. [Mayo Clin., Rochester, Minn.]: Surgical treatment of carcinoma of the right portion of the colon. M. Rec. & Ann. 42: 519-524, June, 1948.

McKittrick, Leland S. [Boston, Mass.]: Principles old and new of resection of the colon for carcinoma. Surg., Gynec. & Obst. 87: 15-25, July, 1948.

Modlin, John [Ellis Fischel State Cancer Hosp., Columbia, Mo.]: Cancer of the colon and rectum. Current trends in surgical management. J. Missouri State M. A. 45: 339-344, May, 1948.

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Paus, Nikolai [Drammen, Norway]: Cancer coli. [Cancer of the colon.] Nord. med. 37: 166-168, Jan. 23, 1948.—Review of 55 patients. Of 38, 23 had 3-yr. cures; 20 of these are still living.—*M. C. J.*

Russo, Armando G.: Cáncer de colon derecho. Hemicolectomía derecha en una etapa. Resultados operatorios. [Cancer of the ascending colon. Right hemicolectomy in one stage. Operative results.] Rev. Asoc. méd. argent. 61: 686-690, Sept. 15-30, 1947.—Seven case reports.

Saltzstein, Harry C. [Detroit, Mich.]: Mesenteric thrombosis of lower ileum following resection of the sigmoid colon for carcinoma. Am. J. Surg. 75: 854-858, June, 1948.—Case report.

Scarborough, Robert A. [San Francisco, Calif.]: California Cancer Commission Studies. Chapter XX. Carcinoma of the colon. California Med. 69: 77-79, July, 1948.

Strauss, Alfred A. [Chicago, Ill.]: Preliminary ileostomy as an important aspect of colon surgery based on thirty years of clinical experience. J. Internat. Coll. Surgeons 11: 178-181, Mar./Apr., 1948.

Swinton, Neil W. [Lahey Clin., Boston, Mass.]: The significance and frequency of benign polyps of the colon and rectum. Am. Pract. 2: 603-605, May, 1948.

Waite, V. C. [The Clinic, Honolulu, Hawaii]: Segmental resection of the colon for carcinoma: development and modern methods. Proc. Staff Meet. Clin., Honolulu 14: 25-31, May, 1948.

Warren, Shields [Harvard M. Sch., Boston, Mass.]: Tumor Seminar. Adeno-acanthoma of the cecum. J. Missouri State M. A. 45: 373-376, May, 1948.

Waugh, John M., & Custer, Monford D., Jr. [Mayo Clin., Rochester, Minn.]: Resection and primary anastomosis for lesions of the left portion of the colon. Postgrad. Med. 3: 85-91, Feb., 1948.

Weisberg, A. Lester [Bronx Hosp., New York City]: Lipoma of the colon causing intestinal obstruction. Am. J. Surg. 76: 116-118, July, 1948.—Case report.

Wyatt, J. P., & Goldenberg, H. [Toronto East Gen. Hosp., Ont.]: Malignancy developing in familial polyposis of colon in male twins. Canadian M. A. J. 58: 603, June, 1948.—Twenty-six yrs. of age.

RECTUM AND ANUS

Andrade, Ernesto: Diagnostico y tratamiento del cáncer rectal. [Diagnosis and treatment of rectal cancer.] Rev. Fac. de med., Bogotá 16: 951-958, Oct., 1947.—A review.

Craig, Marion S., Jr. [Little Rock, Ark.] Prevention of cancer of the rectum and colon: diagnosis and treatment of the precancerous lesions. J. Arkansas M. Soc. 45: 46-49, July, 1948.

Deddish, Michael [Memorial Hosp., New York City]: Rectal and colon survey. Strang Cancer Prevention Clinic—1946. J. Am. M. Women's A. 3: 138-139, Apr., 1948.—Proctosigmoidoscopic examinations were made in 1011 applicants more than 45 yrs. of age or having chronic rectal bleeding: 0.5% had cancer of colon or rectum; 6.0% had polyps (4.6% of females, 6.8% of males); 88% of the lesions were visualized at sigmoidoscopy. Tables are presented of anatomical and sex distribution. Of 68 lesions found, there were 61 polyps, 3 carcinomas, 2 polyps with cancer, 1 carcinoid, 1 myoma.—*D. A. S.*

Gardner, Campbell [Montreal, Que.]: Problems in the treatment of carcinoma of the rectum. Canadian M. A. J. 58: 454-457, May, 1948.

Graham, A. Stephens [Richmond, Va.]: Current trends in surgery of the distal colon and rectum for cancer. Ann. Surg. 127: 1022-1034, May, 1948.—A survey, by questionnaire, of the opinions of 50 surgeons.

Gross, Joseph M. [Beth-El Hosp., New York City]: Basal cell carcinoma of anus. New York State J. Med. 48: 1162-1163, May 15, 1948.—Case report.

Guzauskas, Anthony: Carcinoma of rectosigmoid with unusual polyps. Proc. Inst. Med. Chicago 17: 93-94, Apr. 15, 1948.—Case report.

Lahey, Frank H. [Lahey Clin., Boston, Mass.]: Abdominoperineal removal of the rectum versus preservation of the sphincter and pull-through operations. Lahey Clin. Bull. 5: 226-231, Apr., 1948.

Li, Irene Y. [Columbia Univ., Coll. Phys. & Surgeons, New York City]: Benign lymphoma of the rectum. Surgery 23: 814-820, May, 1948.—Report of 26 cases plus 23 from the literature.

Macdonald, I. B., & Aberhart, C. [Toronto Gen. Hosp., Ont.]: The neurogenic origin of bladder symptoms following proctectomy. Canadian M. A. J. 58: 450-451, May, 1948.—From cystoscopic study of 12 patients the authors conclude that the bladder-neck lesion following radical proctectomy is neurogenic in origin.—*D. A. S.*

McLanahan, Samuel, & Gilmore, William E. [Johns Hopkins Univ. Sch. Med., Baltimore, Md.]: Colostomies: a follow-up study of functional results. South. M. J. 41: 408-412, May, 1948.

Mayo, Charles W., & Smith, Robert S. [Mayo Clin., Rochester, Minn.]: Low anterior segmental resection with or without colostomy. Ann. Surg. 127: 1046-1055, May, 1948.—Review of 200 cases.

Nicole, R. [Basel, Swtz.]: Operation des Rectumkarzinoms mit Sphinktererhaltung. [Operation for carcinoma of the rectum with preservation of the sphincter.] Helvet. chir. acta 14: 379-385, Oct., 1947.—A review.

Pettavel, C. A. [Neuchâtel, Swtz.]: Résultats immédiats de l'amputation périnéo-abdominopérinéale du rectum selon le procédé de Decker. [Immediate results of perineoabdominoperineal amputation of the rectum by Decker's procedure.] Helvet. chir. acta 14: 375-378, Oct., 1947.—A review.

Schatter, Ranered [Berlin, Germany]: Die Rontgen-Nahbestrahlung der Rectum-Karzinome. [Contact (Chaoul) roentgen-ray irradiation of carcinoma of the rectum.] Strahlentherapie 77 (2): 211-216, 1947.—A review.

Schneider, Henry C. [M. Director, United Am. Mechanics, Philadelphia, Pa.]: Diseases of the anus, rectum and sigmoid colon: their relationship to life expectancy. J. Insurance Med. 3: 21-22, Dec./Jan./Feb., 1947/48.

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LIVER AND BILIARY TRACT

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Danzis, Max [Newark Beth Israel Hosp., N. J.]: Carcinoma of the gall bladder. A report of 26 cases. J. M. Soc. New Jersey 45: 274-277, June, 1948.—One patient survived 5 yrs.

Dumont, R. [Hôp. civil d'Ixelles, Belg.]: **Présentation d'un cas clinique de tumeur du foie.** [Case of tumor of the liver.] Acta gastro-enterol. belg. 11: 160-164, Mar., 1948.—Hepatoma.

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Siler, Vinton E., & Zinninger, Max. M. [Univ. Cincinnati Coll. Med., Ohio]: **Surgical treatment of carcinoma of the ampulla of Vater and the extrahepatic bile ducts.** Arch. Surg. 56: 199-223, Feb., 1948.—Analysis of 8 ampullary carcinomas and 10 extrahepatic bile-duct carcinomas.

Vignalou, Jean [Hôp. Paris, France]: **Cancer de l'ampoule de Vater.** [Cancer of the ampulla of Vater.] Hôpital 36: 36-38, Feb., 1948.—Case report.

PANCREAS

Cole, Warren H. [Univ. Illinois Coll. Med., Chicago]: **Surgical lesions of the pancreas.** Nebraska State M. J. 33: 195-202, June, 1948.

Jennings, W. K., & Russell, William O. [Univ. South. California M. Sch., Los Angeles]: **Phlebothrombosis associated with mucin-producing carcinomas of the tail and body of the pancreas. A clinicopathologic study of two cases with necropsy.** Arch. Surg. 56: 186-198, Feb., 1948.—Multiple venous thrombi occurred in portal and systemic circulations in each case. —*D.A.S.*

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Silver, Gershon B., & Lubliner, Ruth K. [Montefiore Hosp., New York City]: **Carcinoma of the pancreas. A clinicopathologic survey.** Surg., Gynec. & Obst. 86: 703-716, June, 1948.—A series of 104 cases of carcinoma of the pancreas, which comprised 3.8% of all necropsies at Montefiore Hospital from 1919 to 1946, is reviewed. Because of clinical and pathological differences, the cases are divided into 2 groups. 55% of the carcinomas arose in the head and neck of the pancreas. Initial symptoms in this group were weight loss in 65%, pain in 49%, anorexia in 44%, with jaundice being present in only 25%. When the carcinoma arose in the body or tail (41% of all cases), the initial symptoms were weight loss in 72%, pain in 70%, weakness in 42%, and jaundice in none of the cases. The importance of pain as an early symptom is stressed. At autopsy, 18% of cases with the carcinoma arising in the head and neck were still free of metastasis in contrast to the body-tail group in which only 5% were free of metastases. 2 cases each of carcinoma arising in aberrant pancreas and islet-cell carcinoma made up the remainder of the series. Distortion, displacement, or obstruction of the duodenum and stomach on x-ray examination are frequently present, usually of an extrinsic nature.—*L. W. Guiss, M.D.*

Thorling, Leif [Uppsala, Sweden]: **Spontanhypoglykämi—insulom.** [Spontaneous hypoglycemia—insuloma.] Nord. med. 37: 217-218, Jan. 30, 1948.—Case report.

Ulett, George, & Parsons, E. H. [Washington Univ. Sch. Med., St. Louis, Mo.]: **Psychiatric aspects of carcinoma of the pancreas.** J. Missouri State M. A. 45: 490-493, July, 1948.—Three case reports.

Waugh, John M. [Mayo Clin., Rochester, Minn]: **Radical resection of head of pancreas and total pancreatectomy.** J. A. M. A. 137: 141-144, May 8, 1948.—The end results of 49 modified Whipple operations, including 6 cases of total pancreatectomy, are presented. There were 13 deaths (over-all operative mortality, 26%); for the 6 total pancreatectomies, 1 death (16%). 11 operations were for benign disease (islet-cell tumors, 3; chronic pancreatitis with calcification and intractable pain, 8) with a high operative mortality of 45%—attributed to technical difficulties because of the chronic inflammation present. In the group with cancer (head of the pancreas, 19; ampulla of Vater, 16; duodenum, 2; primary carcinoma of the stomach with extension into the head of the pancreas, 1), the operative mortality was 21%; but with the 1-stage operation, only 13%. Of 14 patients with carcinoma of the head of the pancreas who survived the operation, 11 were dead of recurrence in an average time of 8.4 mos.; 3 (2 with lymph-node involvement) were alive an average of 18 mos. Of 8 who survived resection for carcinoma of the ampulla of Vater, 3 died of recurrence; 5 were alive an average of 28 mos., a much more encouraging figure. The operative techniques favored are end-to-end pancreaticojejunostomy; end-to-side choledochojejunostomy; end-to-side postcolic, antiperistaltic gastrojejunostomy; or if total pancreatectomy is done, an end-to-end choledochojejunostomy, with end-to-side-postcolic, antiperistaltic gastrojejunostomy. —*L. W. Guiss, M. D.*

ENDOCRINE ORGANS

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Aires, Argentina]: Anatomia patológica de dos casos de miastenia grave. (Un timoepitelioma y una hiperplasia del timo.) [Pathological anatomy of two cases of myasthenia gravis. (An epithelioma of the thymus and a hyperplasia of the thymus.)] Rev. Asoc. méd. argent. 61: 661-666, Sept. 15-30, 1947.

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ADRENAL

lwall, Nils, & Wulff, H. B. [Univ. Hosp., Lund, Sweden]: A case of suprarenal pheochromocytoma clinically diagnosed and cured by operation. Acta chir. Scandinav. 96(4): 337-344, 1948.

rmstrong, C. N., & Simpson, John [Roy. Victoria Infirmary, Newcastle-upon-Tyne, Eng.]: Adrenal feminism due to carcinoma of the adrenal cortex. A case report and review of the literature. Brit. M. J. 1: 782-784, Apr. 24, 1948.

Broster, L. R., & Patterson, Jocelyn [Charing Cross Hosp., London, Eng.]: An unusual case of adrenal carcinoma, with a note on the application of a new colour test. Brit. M. J. 1: 781-782, Apr. 24, 1948.

Calvi, Leone [Milan, Italy]: Tessuti ipernefroidi in sede atipica. [Aberrant adrenal tissue.] Tumori 21 (4/5): 196-203, 1947.—Two case reports.

Colston, J. A. Campbell [Johns Hopkins Hosp., Baltimore, Md.]: Surgical aspects of bilateral familial pheochromocytoma. J. Urol. 59: 1036-1060, June, 1948.—Two case reports.

Crooke, A. C. [London Hosp., Eng.]: The endocrine disorders associated with Cushing's syndrome and virilism. Report of an unusual case. J. Clin. Endocrinol. 7: 787-794, Dec., 1947.—An unusual case is described of a woman who developed Cushing's syndrome with spontaneous remission. Subsequently she developed the clinical picture of virilism associated with an adrenal cortical carcinoma. Details of the necropsy are given. The endocrine disturbances responsible for Cushing's syndrome and virilism are discussed.—*Auth. Summ.*

Ganem, Emil J., & Cahill, George F. [Columbia-Presbyterian M. Center, New York City]: Pheochromocytomas coexisting in adrenal gland and retroperitoneal space, with sustained hypertension. Report of a case with surgical cure. New England J. Med. 238: 692-697, May 13, 1948.

Guarneri, Victor, & Evans, James A. [Lahey Clin., Boston, Mass.]: Pheochromocytoma. Report of a case, with a new diagnostic test. Am. J. Med. 4: 806-813, June, 1948.—Initial fall of blood pressure followed by marked and more sustained hypertension resulting from subcutaneous injection of 25 mg. mecholyl.—*D.A.S.*

Hartl, Hermann [Allg. öffent. Krankenh., Linz, Austria]: Zur Kasuistik der Nebennierenrindentumoren. [Casuistics of tumors of the suprarenal capsule.] Krebsarzt 3: 178-182, May, 1948.—Two case reports.

Tchékoff, S. [Hôp. Paris, France]: Indications pratiques de la surrénalectomie. [Practical indications for adrenalectomy.] Rev. gén. de clin. et de thérap. 61: 511-513, Nov. 13, 1947.

Wilkins, Lawson [Johns Hopkins Univ. Sch. Med., Baltimore, Md.]: A feminizing adrenal tumor causing gynecomastia in a boy of five years contrasted with a virilizing tumor in a five-year-old girl. J. Clin. Endocrinol. 8: 111-132, Feb., 1948.—This is the first reported case of gynecomastia in a boy due to adrenal tumor before puberty. The marked gynecomastia diminished after removal of an encapsulated adrenal cortical adenoma. After 4 yrs. there is no evidence of recurrence. The daily excretion of 17-ketosteroids was 4 mg., with small amounts of estrogen.

The girl showed enlargement of the phallus, precocious growth of sexual hair, seborrhea, deepened voice, somatic and muscular growth, and accelerated epiphyseal development over a 6-mo. period. An encapsulated cortical tumor was removed; death occurred 2 yrs. later with abdominal metastasis. She excreted 22 mg. of 17-ketosteroids before operation and 124 mg. after recurrence. Microscopically both tumors had large, polyhedral cells with deep-staining and granular cytoplasm with no vacuoles. Fuchsinophilic granules (Broster-Vines stain) were present in both tumors. 70 cases of cortical adrenal tumor in children less than 12 yrs. of age are reviewed and classified according to symptoms of excessive androgen and cortin. Metastasis occurred in 30. Only 14 of 35 in whom removal was attempted were cured.—*J. M. Sether, M.D.*

FEMALE GENITAL TRACT

Bell, Cooper; Jansen, Louisa, & Pettit, Mary Dewitt [Woman's M. Coll. Pennsylvania, Philadelphia]: A report of two cases of multiple primary neoplasms. J. Am. M. Women's A. 3: 149-151, Apr., 1948.—Cervical and vulvar carcinoma; carcinoma of the cecum and cervix.

Hamilton, John D., & Klotz, M. O. [Kingston, Ont.]: **The vaginal smear technique for diagnosis of cancer in the female genital tract.** Canadian M. A. J. 59: 42-47, July, 1948.

Miller, Norman F. [Univ. Mich. Hosp., Ann Arbor, Mich.]: **Carcinoma of the uterus, ovary and tube.** J. A. M. A. 136: 163-169, Jan. 17, 1948.—The author's opinions are based on the personal observations of more than 3000 cancers of the female generative organs during a 27-yr. period. Cancer of the cervix is the most common (65%). Most are advanced when first seen, due to lack of periodic examinations and delay by the patient. However, better than a 40% 5-yr. absolute survival rate is possible—early cases, 75-100%. There is no convincing evidence of a predisposing relationship between the common benign lesions of the cervix and cancer. More than 90% of cervix cancers are epidermoid. The site of origin and mode of spread are discussed. Early preinvasive lesions are commonly asymptomatic. After invasion, the principal symptom is bleeding. About 15% have leukorrhea only. All cases should be biopsied. When adequate facilities become available, vaginal and cervical smear techniques can be useful as a means of screening. The most important single prognostic factor is the clinical extent of growth, classified in 4 groups: I—confined to a small portion of the cervix; II—more advanced but still confined to the cervix; III—questionable extension beyond the cervix; IV—all advanced cases. Histological finding is a less accurate prognostic index. Survival figures for each group are tabulated. The author takes no stand on the question of surgery vs. irradiation but emphasizes the necessity that either be radical and expertly performed. Cancer of the endometrium comprises 15% of the female-generative-tract cancers, occurs most frequently in postmenopausal women, and is generally adenocarcinoma. The commonest symptom is bleeding. The diagnosis is most satisfactorily made by curettage and is best done in the hospital with the patient under anesthesia. The differential diagnosis of vaginal bleeding is discussed. Advanced cases of corpus cancer are treated by x-rays and intracavitary radium. Early cases are best treated by irradiation followed in 6-8 wks. by surgical removal of the entire uterus and adnexa. Ovarian cancer comprises 10-20% of this pelvic group. Owing to lack of symptoms (exception—granulosa-cell tumor), most cases are advanced before discovery. Abdominal enlargement due to the tumor or accompanying ascites, unfortunately, is generally the first evidence. Most occur in postmenopausal women—average age, 52. The degree of malignancy varies considerably. The diagnosis is made by biopsy at abdominal exploration. In most cases both ovaries, tubes, and uterus should be surgically removed, once the diagnosis is definitely established. Pre- and postoperative x-ray therapy is valuable. While, in general, prognosis is not good, it depends largely on the histological type and clinical stage. Early diagnosis of ovarian cancer necessitates periodic pelvic examination. Primary adenocarcinoma of the fallopian tube (0.1% of the group) is briefly considered. A plea is made for earlier diagnosis of all pelvic cancer by frequent periodic examination in the absence of symptoms.—*D.A.S.*

Mocquot, Pr.: L'emploi thérapeutique des hormones sexuelles en gynécologie. [Therapeutic use of sex hormones in gynecology.] Hôpital 35: 184-191, Sept., 1947.—A review.

Musante, Cesarina [Spedali Civili di Genova, Swtz.]: **Fibromioma primitivo peduncolato e torto del legamento largo, ad estrinsecazione addominale.** [Primary pedunculated fibromyoma and torsion of the broad ligament, extra-abdominal.] Minerva med. 2: 420-426, Nov. 17, 1947.—Case report: woman of 56 yrs. The tumor probably derived from the connective tissue of the mesosalpinx or from muscular and connective-tissue rests of embryonal origin. —*M.C.J.*

Otley, Constance M.: A case of multiple cancers. Brit. J. Surg. 35: 441, Apr., 1948.—Breast, cervix, and vulva.

Slovin, Isadore [Wilmington Gen. Hosp., Del.]: **Silberblatt, W. B., & Safford, H. B.: Practical application of the vaginal smear as a method in clinical gynecology.** Delaware State M. J. 20: 109-112, June, 1948.

VULVA AND VAGINA

Duany, Nicolás Puente: Comentarios sobre un caso de epitelioma poliposo, no infiltrante de la vagina. [A noninfiltrating, polypoid epithelioma of the vagina.] Rev. méd. cubana 59: 19-23, Jan., 1948.—Case report.

Duarte, Delio [Belo Horizonte, Minas Gerais, Brazil]: **Hidradenoma e hidradenocarcinoma de vulva.** [Vulvar hidradenoma and hidradenocarcinoma.] Rev. de ginec. e d'obst. 42: 256-260, Apr., 1948.—Case report.

Restrepo, Roberto, & Lemaitre, Alfonso Méndez [Inst. Nac. Radium, Bogotá, Colombia]: **Infecciones amibianas confundidas con cáncer. Amibiasis del cuello uterino y vagina diagnosticada como cáncer uterino avanzado. Amibiasis de la vulva.** [Amebic infections confused with cancer. Amebiasis of the cervix & vagina diagnosed as advanced uterine cancer. Amebiasis of the vulva.] Rev. Fac. de med., Bogotá 16: 914-920, Sept., 1947.

CERVIX

Arneson, A. N. [Barnard Free Skin & Cancer Hosp., St. Louis, Mo.]: **Prognosis in carcinoma of the uterine cervix.** J. Tennessee State M. A. 41: 195-205, June, 1948.

Boveri, José L., & Cid, José [Rosario, Argentina]: **Fibro-mixo-condrosarcoma del cuello uterino.** (Resumen.) [Fibromyxochondrosarcoma of the cervix. (Résumé.)] Obst. y ginec. latino-am. 5: 644-645, Dec. 31, 1947.—Case report.

Crou, Roland S. [Marquette Univ. Sch. Med., Milwaukee, Wis.]: **The treatment of carcinoma of the cervix.** Wisconsin M. J. 47: 480-482, May, 1948.

Galloway, Charles Edwin [Northwestern Univ. M. Sch., Chicago, Ill.]: **Early diagnosis of cervical carcinoma.** Mississippi Valley M. J. 70: 93-97, May, 1948.

Hess, Paul, & Proppe, Albin [Duisburg, Germany]: **Die Strahlenbehandlung des Kollumkarzinoms. [Irradiation of carcinoma of the cervix.]** Strahlentherapie 77 (2): 199-210, 1947.—The results of 131 cases, seen between 1934-1942, with evaluation of the Ra and x-ray dosage employed.—*M.C.J.*

Oliveira, Carlos Alberto B., de [Salvador, Est. de Bahia, Brazil]: **Câncer do côto cervical prolabado. [Cancer of the prolapsed cervical stump.]** Rev. de ginec. e d'obst. 42: 220-223, Mar., 1948.—Case report: spindle-cell carcinoma.

Moschino, A., & Narpozzi, A. [Univ. Padova, Italy]: **La fosfatasi nel cancro dell'utero. Noto 2ª. Il comportamento della fosfatasi serica nella radiumterapie del carcinoma del collo. [Phosphatase in uterine cancer. 2a. The behavior of serum phosphatase in radium therapy of cervical cancer.]** Riv. d'ostet. e ginec. prat. 29: 202-205, Oct., 1947.

Nector, Lee T. [Tampa, Fla.]: **Cervical lesions—diagnosis of malignant disease by vaginal smear.** J. Florida M. A. 34: 654-657, May, 1948.

Scapier, Joseph [Strang Cancer Prev. Clin., New York City]: **Diagnosis of cancer by the Papanicolaou smear method.** J. Am. M. Women's A. 3: 139-142, Apr., 1948.—Methods of obtaining vaginal, cervical, and endometrical smears are described, together with criteria for classification. Of 4160 cervical and vaginal smears on new patients in 1946, 14 were diagnosed "positive" or "highly suspicious" for carcinoma: 13 were confirmed by biopsy. A false negative result is reported in only 1 case.—*D. A. S.*

Schmitz, Herbert E. [Mercy Hosp. Inst. Radiation Therapy, Chicago, Ill.]: **The treatment of cervix carcinoma with radium and 800 kilovolt x-ray.** Am. J. Obst. & Gynec. 55: 262-272, Feb., 1948.—Of 422 cases occurring between 1933 and 1942, 166 (that had no treatment before admission) are analyzed. According to the author's classification of clinical grouping, 70% were unfavorable cases. 2.4% were adenocarcinomas. The techniques of x-ray and radium therapy are described. The attempted tumor dosage was 4000 r and 4500 mg.-hr. respectively. The Werthcim operation was reserved for cases refractory to irradiation. 5-yr. survivals were: group I—11 cases, 90.9%; group II—37 cases, 72.7%; group III—70 cases, 42.85%; group IV—48 cases, 10.43%.—*F. S. Butler, M. D.*

Spitz, Sophie [Memorial Hosp., New York City]: **Progress in the diagnosis of cervical cancer.** J. Am. M. Women's A. 3: 144-145, Apr., 1948.—The detection of 8 cases of noninfiltrating carcinoma of the cervix in the Strang Clinic during 1946 indicates not only that this lesion is rather common but that the methods for its diagnosis are readily available. These methods are discussed.—*D. A. S.*

Ulfelder, Howard [Massachusetts Gen. Hosp., Boston]: **The use of the vaginal smear in the diagnosis of cancer.** Connecticut State M. J. 12: 513-514, June, 1948.

Wallon, Émile [Centre anticancér. Salpêtrière, Paris, France]: **Sur la technique de la curiethérapie des cancers du col de l'utérus. [Technique of radium therapy in cancer of the cervix.]** Presse méd. 56: 244-245, Mar. 31, 1948.

UTERUS

Blumer, C. E. M. [Staffordshire Gen. Infirmary, Eng.], & Edwards, J. L.: **"Mesodermal mixed" tumour of uterus.** J. Obst. & Gynaec. Brit. Emp. 55: 309-311, June, 1948.—Case report.

Boveri, José L., & Lavarello, Adolfo [Rosario, Argentina]: **Porvenir obstétrico de la miomectomizadn. [Obstetrical management of the myomectomized.]** Obst. y ginec. latino-am. 5: 673-676, Dec. 31, 1947.

Chastrusse, & Mahan: **Onze cas de myomectomies pendant la grossesse et le travail. [Eleven cases of myomectomy during pregnancy and labor.]** Rev. franç. de gynéc. et d'obst. 42: 311-323, Nov., 1947.—The authors recommend no operation during pregnancy, if possible, but if operation becomes necessary, the fibroma only should be removed, the pregnancy maintained, progesterone proving useful here. Myomectomy at the beginning of labor is admissible.—*From Auth. Summ.*

Cimberle, Emilio [Univ. Padova, Italy]: **Considerazioni sulle cause delle meno e metrorragie nei fibromi sottomucosi dell'utero. [The cause of meno- and metrorrhagia in submucous fibromas of the uterus.]** Riv. d'ostet. e ginec. prat. 29: 251-255, Nov., 1947.—Six case reports.

Cromer, J. Keith [Warwick Memorial Clin., Washington, D. C.]; Platt, Lois I., & Winship, Theodore: **The colpocytological (Papanicolaou) method of diagnosis of uterine cancer. A preliminary report.** M. Ann. District of Columbia 17: 272-276, May, 1948.

Kullander, Stig [King Gustavus V Jubilee Clin., Lund, Sweden]: **Chorionepithelioma treated with stilboestrol.** Lancet 1: 944-945, June 19, 1948.—Case report.

Lisa, James R.; Hartmann, Hans; Bayer, Irving, & Bonar, Lloy DeF. [Doctors Hosp., & Goldwater Memorial Hosp., New York City]: **Carcinosarcoma of the uterus.** Ann. Surg. 127: 738-744, Apr., 1948.—Report of 2 cases and review of the literature.

McGill, Ralph A. [Tulsa, Okla.]: **Carcinoma of the body of the uterus.** J. Oklahoma State

M. A. 41: 177-180, May, 1948.—General discussion.

McGoogan, Leon S., & Hunt, Howard B. [Univ. Nebraska Coll. Med., Omaha]: **Treatment of carcinoma of the fundus uteri.** Arch. Surg. 56: 172-177, Feb., 1948.—Discussion and analysis of 35 cases.

McSweeney, Daniel J., & McKay, Donald G. [Boston Univ. Sch. Med., Mass.]: **Uterine cancer: its early detection by simple screening methods.** New England J. Med. 238: 867-870, June 17, 1948.

Martin, Joseph P. [Howard Univ. Coll. Med., Washington, D. C.]: **The etiology of fibromyomata of the uterus. Part I: A review of the literature and preliminary comments on the Hartman-Littrell technique of assay.** J. Nat. M. A. 40: 49-58, Mar., 1948.

Mishler, Howard V., & Dickerhoof, Gilbert R. [St. John's Hosp., Cleveland, Ohio]: **Hydatidiform mole in a twin pregnancy with a viable foetus.** Ohio State M. J. 44: 714-715, July, 1948.—Case report.

Moschino, Alcide [Univ. Padova, Italy]: **Le fosfatasi nel cancro dell'utero. Nota III. Il sistema fosfatasico tissulare.** [**Phosphatase in uterine cancer. III. The tissue phosphatase system.**] Riv. d'ostet. e ginec. prat. 29: 187-191, Oct., 1947.

Perry, Thomas, Jr. [Rhode Island Hosp., Providence]: **Sarcoma of the uterus. A report of eighteen cases.** New England J. Med. 238: 793-799, June 3, 1948.

Trapl, Jiri [Charles Univ., Prague, Czechoslovakia]: **Vaginal hysterectomy for cancer of the uterus and vagina.** J. Obst. & Gynaec. Brit. Emp. 55: 303-308, June, 1948.

OVARY AND FALLOPIAN TUBE

Barger, James D.; Edwards, Jesse E.; Parker, Robert L., & Dry, Thomas J. [Mayo Clin., Rochester, Minn.]: **Cardiac clinics. CXXII. Atrial septal defect: presentation of a case with obstructive pulmonary vascular lesions caused by metastatic carcinoma.** Proc. Staff Meet., Mayo Clin. 23: 182-192, Apr. 14, 1948.—In a 64-yr.-old woman with a large congenital atrial septal defect, death resulted from cardiac failure because of pulmonary hypertension consequent to obstructive lesions of the pulmonary arteriolar bed resulting from metastatic adenocarcinoma of the right ovary.—*D. A. S.*

Bassan, David, & Boden, Alfredo [Rosario, Argentina]: **Hemoperitoneo por folículo sangrante. Torsión crónica de un cistoadenoma del ovario.** [**Hemoperitoneum because of a bleeding follicle. Chronic torsion of a cystadenoma of the ovary.**] Obst. y ginec. latinoam. 5: 667-669, Dec. 31, 1947.—Case report.

Bloom, Homer, & Yohe, William [Easton Hosp., Easton, Pa.]: **Papillary cystadenoma attached to the transverse colon. Case report.** Staff Bull. Easton Hosp. 1: 24-27, June, 1948.

Chalmers, J. A. [Roy. Northern Infirmary, Inverness, Scotland]: **Hydatidiform mole in the fallopian tube.** J. Obst. & Gynaec. Brit. Emp. 55: 322-324, June, 1948.—Case report.

Durham, R. B.; Adcock, D. F., & Sweatman, C. A. [Columbia, S. C.]: **A case of dysgerminoma with description of recurrence.** J. South Carolina M. A. 44: 190-192, June, 1948.

Enge, Ludwig A. [Stanford Univ. Sch. Med., San Francisco, Calif.]: **Six cases of primary carcinoma of the fallopian tube.** West. J. Surg. 56: 334-345, June, 1948.

Gaudrault, Gerard L. [Concord Hosp., Concord, N. H.]: **Papillary cystadenocarcinoma of both ovaries. Report of a case with apparent cure eight years after operation.** New England J. Med. 239: 56-57, July 8, 1948.

Gögl, Hermann [Univ. Innsbruck, Austria]: **Zur Frage der Arrhenoblastome.** [**Arrhenoblastomas.**] Krebsarzt 3: 182-190, May, 1948.—A review.

Henderson, D. N. [Univ. Toronto, Ont.]: **Ovarian tumors.** Bull. Vancouver M. A. 24: 210-216, Mar., 1948.

Long, Albert E. [Stanford Univ. Sch. Med., San Francisco, Calif.]: **Hemothorax in relation to benign pelvic tumors.** California Med. 68: 383-387, May, 1948.—Case report: masculinizing and feminizing tumor of the ovary (classified as mesenchymoma).

Montgomery, John B. [Jefferson M. Coll Hosp., Philadelphia, Pa.]: **Malignant tumors of the ovary.** Am. J. Obst. & Gynec. 55: 201-217, Feb., 1948.—Analysis of 107 cases.

Oliver, Howard M. [Mary Hitchcock Hosp., Hanover, N. H.], **& Horne, Elwood O.: Primary teratomatous chorionepithelioma of the ovary. Report of a case.** New England J. Med. 239: 14-16, July 1, 1948.

Paracchi, Piero, & Gallico, Edoardo [Inst. Naz. Studio e Cura dei Tumori, Milan, Italy]: **Nuove ricerche sulla gonodotropinuria nei tumori ovarici.** [**Gonadotropinuria in ovarian tumors.**] Tumori 21 (4/5): 264-273, 1947.—Case report.

Rieben, Guido [Univ.-Frauenklin. Basel, Swtz.]: **Zur Prognose des Disgerminoma ovarii, ein Rückblick auf 23 Fälle.** [*Prognosis of dysgerminoma ovarii, a review of 23 cases.*] Schweiz. med. Wchnschr. 78: 276-282, Mar. 27, 1948.—The literature is reviewed and 23 author's cases added. [Age incidence of the total 168 cases ranged from 6-70 yrs., 111 between 11-25 yrs., 46 between 16-20 yrs.] Of 15 of the author's cases treated 5 or more yrs. ago, 7 are living and free of recurrence. Judging by the clinical course, 7 were benign, 7 malignant; 1 died of pneumonia shortly after operation and neither clinical course nor anatomical findings re-

vealed its type. Site was primarily the right ovary; familial frequency was found. In 3, the tumor was discovered sub partu, on cesarean delivery. Secondary cyst formation is not rare. At present there are no definite criteria for prognosis of any one case. Whether the regressive changes in cells that have ruptured into the blood stream is of value as an indication of immunity (Foederl) and for prognosis cannot be said; nor is the excretion of gonadotropins of value. The primary dysgerminoma, the recurrences, and the metastases are usually x-ray sensitive; dysgerminomas in older patients seem less sensitive. The entire abdomen should be irradiated in postoperative prophylactic or curative x-rays, even when lympth-node metastases are not suspected. Unless this is done, the later appearance of metastases in the peritoneum or lymph nodes of the retroperitoneal space cannot be taken to indicate failure of x-rays. The author obtained a 46.6% 5-yr. cure (but only 29.1% for other malignant ovarian tumors). The poorer prognosis in older patients is indicated statistically. Prognosis can be improved by postoperative irradiation and early recognition of metastases. The blood sedimentation rate is of assistance [in all cases high: 17-150 mm. (av. 30-50 mm.) in 1st hr.]. In contrast to other ovarian blastomas, daughter dysgerminomas usually respond well to x-ray treatment.—*From Auth. Summ.*

Spurney, Paul M. [Polyclin. Hosp., Cleveland Ohio]: **Fibroma of the ovary with ascites and hydrothorax.** Ohio State M. J. 44: 722, July, 1948.—Case report.

Verschure, J. C. M., & Lips, A. C. M. [Utrecht, Neth.]: **Syndroom van Meigs. Goedaardig ovariumgezwel met hydrothorax en ascites. [Meigs syndrome. Benign tumor of the ovary, with hydrothorax and ascites.]** Nederl. tijdschr. v. geneesk. 92: 107-110, Jan. 10, 1948.—Case report; recovery after removal of fibromyoma.—*M. C. J.*

GENITOURINARY TRACT

Greene, Laurence F. [Mayo Clin., Rochester, Minn.]: **Clinical significance of gross hematuria.** Minnesota Med. 31: 651-652, June, 1948.

Herbst, William P., Jr., & Bagley, Clifford E. [Georgetown Univ. Sch. Med., Washington, D. C.]: **Observations in the use of inositol in advanced malignancy of the genito-urinary tract.** J. Urol. 59: 595-598, Apr., 1948.—Inositol was used in 13 patients with advanced cancer. The cases of carcinoma of the prostate, carcinoma of the penis, and seminoma of the testicle, all with metastasis, as far as we could determine from their clinical course, did not receive any beneficial results from the use of inositol. However, the cases of carcinoma of the bladder were definitely influenced as manifested by the disappearance of hematuria and a reduction in size of the original tumor growth. There was 1 case of hypernephroma of the kidney which has had a symptomatic response to this drug. A number of these patients are still receiving the medication and will be brought back for periodic checkups.—*Auth. Summ.*

Nesbit, Reed M., & Lapides, Jack [Univ. Michigan M. Sch., Ann Arbor]: **Hormones in urology.** North Carolina M. J. 9: 173-179, Apr., 1948.

KIDNEY

Antopol, William, & Goldman, Lester [Newark Beth Israel Hosp., N. J.]: **Subepithelial hemorrhage of renal pelvis simulating neoplasm.** Urol. & Cutan. Rev. 52: 189-195, Apr., 1948.—Seven case reports.

Atherton, Lytle [Louisville, Ky.]: **Therapy from standpoint of surgery and radiation.** Kentucky M. J. 46: 285-287, July, 1948.

Bowen, J. Andrew [Louisville, Ky.]: **Tumors of the kidney, classification and general considerations.** Kentucky M. J. 46: 282-283, July, 1948.

Brandenburg, Wolfgang: **Beitrag zur Frage seltener Nierentumoren. (Neurinom der Niere.) [Rare tumors of the kidney (neurinoma of the kidney).]** Zentralbl. f. allg. Path. u. path. Anat. 83 (7/8): 286-289, 1947.—Case report. The tumor was almost entirely neurinoma but at one point the subcapsular cortical substance showed a small papillary adenoma containing tiny islands of adrenal-cortex tissue. The adenoma was directly beside a large neurinoma nodule with no connective-tissue delimitation between the two, although they did not seem to merge with one another. Based on Apitz's work, the author concludes that the neurinoma of the kidney (not hitherto observed) is to be considered a developmental disturbance.—*M. C. J.*

Ferris, Deward O., & Daut, Richard V. [Mayo Clin., Rochester, Minn.]: **Epithelioma of the pelvis of a solitary kidney treated by electrocoagulation.** J. Urol. 59: 577-579, Apr., 1948.—Case report.

Gordon, Benjamin S. [Veterans Adm. Hosp., New York City]: **Tubule adenoma of the kidney.** J. Urol. 59: 1019-1021, June, 1948.—Case report.

Hanley, Howard G. [St. Paul's Hosp., London, Eng.]: **Perirenal tumours. With a report of a further case of perirenal fibrosarcoma.** Brit. J. Surg. 35: 406-410, Apr., 1948.

Heckel, Norris J., & Penick, George D. [Presbyterian Hosp. Chicago, Ill.]: **A mixed tumor of the kidney: lipo-myo-hemangioma.** J. Urol. 59: 572-576, Apr., 1948.—Case report.

Irazu, Juan: **Adenoma papilar de riñón. Hipertensión renal. [Papillary adenoma of the kidney. Renal hypertension.]** Prensa méd. argent. 35: 436-439, Mar. 12, 1948.

Liavaag, Kaare [Oslo, Norway]: **Om nyrebekkenpapillomer. [Papilloma of the renal pelvis.]** Nord. med. 37: 131-134, Jan. 16, 1948.—Four case reports; 3 patients seen 1946, 1947. One patient, first operated upon in 1942, developed a papilloma of the stump of the ureter and sub-

sequently (1944) cancer of the bladder. The author recommends nephrectomy and total ureterectomy.—*M. C. J.*

Lockwood, Ira H.; Smith, Arthur B., & Walker, John W. [Research Clin., Kansas City, Mo.]: **Diagnosis of lesions of the upper portion of the urinary tract. Fundamental concepts.** J. A. M. A. 137: 516-519, June 5, 1948.

Mann, Lewis T. [Mt. Sinai Hosp., New York City]: **Spontaneous disappearance of pulmonary metastases after nephrectomy for hypernephroma. Four year follow-up.** J. Urol. 59: 564-566, Apr., 1948.—Case report.

Neibling, Harold A., & Walters, Waltman [Mayo Clin., Rochester, Minn.]: **Adenocarcinoma and tuberculosis of the same kidney: review of the literature and report of seven cases.** J. Urol. 59: 1022-1035, June, 1948.

Pearse, Robin [Toronto Gen. Hosp., Ont.]: **Malignant adenoma of the kidney.** J. Urol. 59: 553-556, Apr., 1948.—Case report.

Spence, Harry M.; Baird, Sydney S., & Fuqua, Foster [Dallas M., & Surg. Clin., Texas]: **The surgical management of hypernephroid tumors of the kidney ("hypernephroma").** South. M. J. 41: 495-501, June, 1948.—Discussion and 5 case reports.

Taylor, John A. [New York City]: **Extensive metastasizing hypernephroma associated with massive bilateral adenoma of the adrenal.** J. Urol. 59: 557-563, Apr., 1948.—Case report.

Townsend, John M. [Louisville, Ky.]: **Clinical manifestations of renal neoplasm.** Kentucky M. J. 46: 283-285, July, 1948.

Turkel, Eric F. [Greenville, Miss.]: **Hemangioma of the kidney.** J. Urol. 59: 802-806, May 1948. —Case report.

URETER

Fagerstrom, Dudley P. [San Jose, Calif.]: **Proliferative tumors of the ureter and renal pelvis, with further observations on the significance of "epithelial cell nests": six case reports.** J. Urol. 59: 333-357, Mar., 1948.—The conflicting views as found in the literature relating to epithelial crypts, buds, and nests are briefly presented. Microscopic investigation of the ureters removed from 120 autopsies was carried out in order to study these epithelial aberrances in their incipient stage, and to determine if possible their etiological significance in solid and cystic tumors of the ureteral mucosa. 6 clinical patients presenting various types of mucosal neoplasms are discussed, and the microscopic findings in the surgical specimens correlated with the epithelial changes found in the autopsy series. Hyperplasia of the urinary epithelium may result from local irritation, such as chronic infection, or from noxious agents circulating in the body fluids. Epithelial buds and crypts are but bizarre expressions of epithelial hyperplasia. The theory of "cell nest" formation, as proposed by von Brunn and accepted by most present-day writers, is not supported by this study.—*Auth. Summ. & Concl.*

Gualtieri, Thomas; Hayes, James J., & Segal, Abraham D. [New York City]: **Report of two cases of carcinoma of the ureter; discussion of the pathogenesis of urinary tract tumors.** J. Urol. 59: 1083-1100, June, 1948.

Presman, David, & Ehrlich, Louis [Cook Co. Hosp., Chicago, Ill.]: **Metastatic tumors of the ureter.** J. Urol. 59: 312-325, Mar., 1948.—Survey of literature. Report of 2 cases: gastric carcinoma and bronchogenic carcinoma.

BLADDER AND URETHRA

Alpert, Henry R. [Veterans Adm. Hosp., Wood, Wis.]: **Primary carcinoma in a diverticulum of the bladder.** Urol. & Cutan. Rev. 51: 680-682, Dec., 1947.—Case report; fibroadenomatous hypertrophy with prostatitis.

***Cawker, C. Agnew** [Shaughnessy Hosp., Vancouver, B. C.]: **Haemangioma of the urinary bladder.** Canadian M. A. J. 59: 63-64, July, 1948.—Case report.

Darget, R. [Bordeaux, France]: **Le traitement des tumeurs malignes de la vessie par l'implantation à vessie ouverte d'aiguilles de radium. [Treatment of malignant bladder tumors by implantation of radium needles into the opened bladder.]** Mém. Acad. de chir. 73 (25/26): 529-530, 1947.—By author's method, he has obtained 38% 5-yr. cures.—*M. C. J.*

Davis, Edwin [Omaha, Nebr.]: **Disappearance of carcinomatous ulceration of bladder following ureterosigmoidostomy. Report of two cases.** J. A. M. A. 137: 450-453, May 29, 1948.

Deakin, Rogers [Washington Univ. Sch. Med., St. Louis, Mo.]: **Cystoscopic fulguration of many papillary carcinomata of the bladder.** Urol. & Cutan. Rev. 51: 669-671, Dec., 1947.

Goodhope, C. D. [Seattle, Wash.]: **Treatment of bladder carcinoma by total cystectomy.** Northwest Med. 47: 341-343, May, 1948.

Higgins, C. C., & Hausfeld, K. F. [Cleveland Clin., Cleveland, Ohio]: **Cutaneous metastases from carcinoma of the urinary bladder: report of 2 cases.** J. Urol. 59: 879-886, May, 1948.

Howard, Allan H., & Bergman, R. Theodore [Los Angeles Co. Gen. Hosp., Calif.]: **Mucous adenocarcinoma of the urinary bladder.** J. Urol. 59: 455-460, Mar., 1948.—Case report and review of literature.

Keyes, Edward L. [New York City]: **Epithelial bladder tumors attacked by radons and fulguration during the years, 1926-1938.** J. Urol. 59: 875-878, May, 1948.

Lich, Robert, Jr., & Grant, Owsley [Univ. Louisville Sch. Med., Ky.]: **The use of estrogens in the treatment of bladder tumors.** J. Urol. 59: 682-686, Apr., 1948.— Eleven instances of vesical neoplasm are reported along with their response to stilbestrol therapy. The most consist-

ent effects were subjective relief and dissolution of papillomata.—*Auth. Summ.*

Mackles, A.; Immergut, S.; Grayzel, D. M., & Cottler, Z. R. [Jewish Hosp. Brooklyn, New York City]: Carcinoma and sarcoma of bladder: report of unusual simultaneous occurrence of both tumors. J. Urol. 59: 1121-1126, June, 1948.

Pearlman, Carl K., & Bobbitt, Ray M. [Veterans Adm. Hosp., Huntington, W. Va.]: Carcinoma within a diverticulum of the bladder. J. Urol. 59: 1127-1129, June, 1948.—Case report.

Raju, R. N., & Rao, P. Rama [Osler Hosp., Podur, West Godavari Dt., India]: Dermoid bladder. J. Indian M. A. 17: 198, Mar., 1948. —Case report.

Savran, J.; Sayer, E. A., & Schradiack, C. E. [Providence, R. I.]: Primary malignant melanoma of female urethra. Am. J. Surg. 75: 743-745, May, 1948.—Case report.

Semple, J. E. [St. Paul's Hosp. Urol. & Skin Dis., London, Eng.]: Papilloma ta of bladder treated with podophyllin. Preliminary report. Brit. M. J. 1: 1235-1237, June 26, 1948.—Four cases of papillomas of the bladder treated with podophyllin in liquid paraffin applied direct to the new growth through a cystoscope are reported and the technique is described. 3 would have required cystotomy and open fulguration, but after a few applications of podophyllin the extent and size of the tumors had diminished so that they were successfully treated by perurethral fulguration. The 4th case showed marked atrophy of the growth, so that perurethral fulguration of the base of the papilloma was alone required. The number of cases in which this method has been carried out is too small to allow any definite conclusions to be drawn, but the results appear to warrant further trial of this drug and those allied to it in action.—*Auth. Summ. & Concl.*

Vose, Samuel N., & Dixey, Grant M. [Boston, Mass.]: Coincidence of carcinoma of the bladder and interstitial cystitis. J. Urol. 59: 580-582, Apr., 1948.—Three case reports.

PROSTATE

Baird, Sydney S., & Hare, Daniel M. [Parkland Hosp., Dallas, Tex.]: Metastasis of prostatic carcinoma to testicle. J. Urol. 59: 1208-1211, June, 1948.—Case report.

Boylan, Richard N., & Tillisch, Jan H. [Mayo Clin., Rochester, Minn.]: The value of combined blood phosphatase and sedimentation rate determinations in the diagnosis of metastasis in prostatic carcinoma. J. Urol. 59: 931-934, May, 1948.—In carcinoma of the prostate gland with skeletal metastasis normal values were found for: acid phosphatase, 34% of cases; the sedimentation rate, 23%; alkaline phosphatase, 14%; combined acid and alkaline phosphatase values and the sedimentation rate, 2%. The sedimentation rate was elevated in 47.7% of the cases of carcinoma of the prostate gland without metastasis. Determination of the sedimentation rate is of some help in the early diagnosis of carcinoma of the prostate.—*Auth. Summ. & Concl.*

Dufour, André [Hôp. Paris, France]: Les indications nouvelles de la prostatectomie. [New indications for prostatectomy.] Hôpital 36: 6-8, Jan., 1948.

Entz, F. Harold [Waterloo, Iowa]: Probable metastatic carcinoma of the male breast following stilbestrol therapy: case report. J. Urol. 59: 1203-1207, June, 1948.

Fergusson, J. D. [Central Middlesex Co. Hosp., Eng.]: The role of oestrogen therapy in the treatment of prostatic cancer. Post Grad. M. J. 24: 312-323, June, 1948.

Fischmann, Joseph; Chamberlin, Harold A.; Cubiles, Ricardo, & Schmidt, Gerhard [Tufts Coll. M. Sch., Boston, Mass.]: Quantitative determinations of acid phosphatase in the prostate under various normal and pathological conditions: preliminary report. J. Urol. 59: 1194-1197, June, 1948.

Grey, Jorge de Moraes [Univ. Brazil, Rio de Janeiro]: Câncer da próstata. [Cancer of the prostate.] Hospital, Rio de Janeiro 33: 335-354, Mar., 1948.—A review.

Hinman, Frank, Jr. [Univ. California M. Sch., San Francisco]: The early diagnosis and radical treatment of prostatic carcinoma. California Med. 68: 338-343, May, 1948.—An analysis is presented of the 45 cases of early carcinoma of the prostate diagnosed by rectal palpation and treated by radical perineal prostatoseminal vesiculectomy in the last 20 yrs. by members of the University of California Hospital staff. 4 factors have been advanced as arguments against the value of the radical operation. We feel that these are answered by the results of the analysis. 1. The difficulty of early diagnosis: It is admitted that early diagnosis may be difficult or impossible, but the one means of obtaining it, rectal palpation, must be exploited to the fullest extent by routine examinations and perineal biopsy of all suspicious lesions. 2. Prohibitive operative mortality: The average mortality rate for published series is between 5 and 6%. In the present series, 13.3% died within 2 mos. of operation, but there were no deaths in the last 20 cases. These rates are felt to be within reason when compared to the rate of cure. 3. High incidence of incontinence: Incontinence occurred in 11% of the cases. This likewise is considered a small price for the high rate of cure. 4. Low rate of cure: Of 23 cases followed 5 yrs. or more, 56.5% lived 5 yrs. 9 are still alive without evidence of carcinoma and 5 died without evidence of recurrence (68.7%). These figures are compared with a large series of unmetastasized untreated cases in which only 6 to 10% survived 5 yrs. The rate of cure for open series of shorter duration likewise is twice as high as for untreated cases and only slightly less than twice as high as a

castrate series. Radical perineal prostatectomy is the indicated procedure, therefore, in the approximately 5% of patients with carcinoma of the prostate who are examined early while the lesion is still limited by the capsule. Every effort must be made to increase the number of patients in this group and to give them radical surgery, since it is the only treatment that is curative.—*Auth. Summ.*

Kilpatrick, F. R. [Guy's Hosp., London, Eng.]: **Carcinoma of the prostate.** Clin. J. 77: 11-13, Jan./Feb., 1948.— Brief general discussion.

King, E. J. [Post. Grad. M. Sch., London, Eng.], **& Delory, G. E.: Acid and alkaline phosphatases in their relation to malignant disease.** Post Grad. M. J. 24: 299-306, June, 1948.

McIntyre, D. W. [Cleveland, Ohio]: **Massive leiomyoma of prostate: case report.** J. Urol. 59: 1198-1202, June, 1948.

May, James A., & Stimmel, Benjamin F. [San Diego, Calif.]: **Do patients with cancer of the prostate gland show abnormal metabolism of therapeutic doses of the natural estrogens?** J. Urol. 59: 396-403, Mar., 1948.—The application of our procedure for the fractionation and photometric estimation of the urinary estrogens (estradiol, estrone, and estriol), in a small series of cases with and without carcinoma of the prostate, following the administration of single therapeutic doses of the natural estrogens, reveals: (a) that there is no consistent difference in the total estrogen excretion; (b) that the presence or absence of the testes appears not to alter the total excretion of estrogens nor the relative distribution of estradiol, estrone, and estriol in the urine; and (c) that the patients with carcinoma of the prostate showed a tendency (75% of 8 cases) to convert exogenous estrone into estriol more readily than did the patients without cancer, only 20% of whom (1 out of 5 patients) behaved in this way.—*Auth. Summ.*

Simonds, James P. [Northwestern Univ. Sch. Med., Chicago, Ill.]: **Serum phosphatase determinations in differential diagnosis and in prognosis.** Mississippi Valley M. J. 70: 109-113, May, 1948.

TESTIS

Farrell, James I., & Atkinson, Robert L. [Evanston Hosp., Evanston, Ill.]: **Metastatic retroperitoneal tumor from an undescended testicle.** Urol. & Cutan. Rev. 51: 646-648, Nov., 1947.—Seminoma; case report.

Gagnon, E. D. [Toronto, Ont.]: **An unusual case of multiple malignancy.** Brit. J. Surg. 35:435-436, Apr., 1948.—Seminoma of testis and adenocarcinoma of ascending colon.

Gill, Richard D., & Howell, Roderick B. [Wheeling Clin., Wheeling, W. Va.]: **Primary bilateral testicular tumor.** J. Urol. 59: 940-947, May, 1948.—Case report: bilateral embryonal carcinoma.

Levant, Benjamin, & Chetlin, Milton A. [Montefiore Hosp., Pittsburgh, Pa.]: **Neurofibroma of tunica albuginea testis.** J. Urol. 59: 1187-1189, June, 1948.—Case report.

Lewis, Lloyd C. [Washington, D. C.]: **Testis tumors: report on 250 cases.** J. Urol. 59: 763-772, Apr., 1948.

Ogilvie, Heneage [Guy's Hosp., London, Eng.]: **Scrotal swellings. Lecture delivered at The Royal College of Surgeons of England on 1st April, 1948.** Ann. Roy. Coll. Surgeons England 2: 219-232, May, 1948.

Wilbur, E. Lloyd, & Burger, Robert A. [Veterans Adm. Hosp., North Little Rock, Ark.]: **Extreme Leydig cell hyperplasia associated with two other endocrine changes. A case report.** J. Clin. Endocrinol. 8: 390-396, May, 1948.

EXTERNAL GENITALIA

Kennaway, E. L. [St. Bartholomew's Hosp., London, Eng.]: **Cancer of the penis and circumcision in relation to the incubation period of cancer.** Brit. J. Cancer 1: 335-344, Dec., 1947.—Cancer of the penis does not occur after circumcision on the 8th day according to the Jewish practice, but occurs in later life in Moslem populations, where the operation is carried out between the 3d and 14th yrs. But no record has been found in the literature of the age-relations in even a single case of cancer of the penis in a Moslem. 16 recorded cases of cancer of the penis following surgical circumcision at a mean age of 23 (range 14 to 45) developed cancer of the penis after a mean interval of 23 yrs. (range 8 to 41 yrs.). The failure of the operation deferred until the 14th yr. to give the protection given by it when carried out on the 8th day suggests that the train of events leading to the malignant growth is set going early in life, and that removal of the cause does not then avert the development of cancer at a much later age. Other forms of cancer are perhaps due to factors acting in youth. Cancer of the penis is very prevalent among some peoples of Asia who do not practice circumcision. The protection given by the Jewish operation is not due to removal of the cancer-bearing area.—*Auth. Summ.*

McCrea, Lowrain E. [Philadelphia, Pa.]: **Angioma of the male urethra: review of the literature—report of a case.** Urol. & Cutan. Rev. 52: 204-205, Apr., 1948.

Sartor, Erland [Surg. Clin., Lund, Sweden]: **Splenic tissue in the scrotum.** Acta chir. Scandinav. 96 (4): 388-392, 1948.—Report of a case and review of 15 in the literature.

Zausner, Joseph [Bellevue Hosp., New York City]: **Penile carcinoma. A review of 43 cases treated at Bellevue Hospital during the past twenty-five years.** Radiology 50: 786-790, June, 1948.

HEMATOPOIETIC SYSTEM

Aisner, Mark [Tufts Coll. M. Sch., Boston, Mass.], **& Hoxie, Thomas B.: Bone and joint pain in**

leukemia, simulating acute rheumatic fever and subacute bacterial endocarditis. New England J. Med. 238: 733-737, May 20, 1948.—Report of 4 cases: acute lymphatic leukemia.

Bernard, Jean: Le traitement chirurgical de la maladie de Hodgkin. [Surgical treatment of Hodgkin's disease.] Sang 18 (8): 483-486, 1947.

Brun, C.: Nouvelle contribution à l'étude de la granulomatose maligne. [Another contribution to the study of malignant granulomatosis.] Sang 18 (9): 571-575, 1947.

Burchenal, Joseph H. [Sloan-Kettering Inst., New York City]: The newer nitrogen mustards in the treatment of leukemia. Radiology 50: 494-499, Apr., 1948.—Two of the new nitrogen-mustard derivatives that have been shown to be effective in prolonging the survival time in mice with transmitted leukemia have now been tried clinically. 1 : 3 propane diamine N N N′ N′ tetrakis (2-chloroethyl) dihydrochloride, commonly known as SK 136, is approximately as toxic as the better-known methyl-bis (2-chloroethyl) amine hydrochloride and is given clinically in a dosage of 0.1 mg./Kg. of body weight daily for 4 to 8 doses. In this dosage it appears to cause less nausea and vomiting. 11 cases of chronic myelogenous leukemia, 2 of subacute myelogenous leukemia, and 19 of acute leukemia have been treated with this drug. The therapy of acute leukemia, although occasionally promising, has by and large been unsatisfactory. In chronic myelogenous leukemia the results were similar to those produced by radioactive phosphorus or x-rays. Although not curative, it seems to be useful to the clinician. In the majority of cases it offers nothing more than skillfully applied x-rays.

Another derivative, 1 : 3 propane diamine 2-chloro N N N′ N′ tetrakis (2-chloroethyl) dihydrochloride, commonly known as SK 137, showed a chemotherapeutic activity approximately that of SK 136 but the appearance of occasional transient toxic psychoses of 12-72 hrs. duration with SK 137 caused its use to be discontinued. This compound had no advantage over SK 136 to offset this added toxic action.—*Auth. Abstr.*

Cazal, P. [Centre reg. Transfusion sang., Montpellier, France]: Analyse cytologique des leucémies à cellules atypiques. Utilité de la formule peroxydasique. [Cytological analysis of atypical-celled leukemias. Usefulness of the peroxydase formula.] Rev. d'hémat. 2 (4): 507-519, 1947.

Chambers, H. D. [Gen. Hosp., Kingston, Jamaica]: Report on a case of leukaemia cutis. Brit. J. Dermat. 60: 211-213, June, 1948.

Chevallier, Paul, & Marinone, G.: Sur un cas de leucémie myéloïde à basophiles. [A case of basophilic myeloid leukemia.] Sang 18 (7): 401-405, 1947.

Connelly, Joseph R.; Smith, James T., & Straughan, Joseph M. [M. C., U. S. Navy]: Hodgkin's disease. U. S. Nav. M. Bull. 48: 180-189, Mar./Apr., 1948.—Review of literature and case report.

Croizat; Revol; Viallet, & Morel: Action remarquable des perfusions sanguines dans un cas cryptoleucémie aiguë. Normalisation passagère de la moelle et du sang. [Notable effect of blood transfusion in a case of acute cryptoleukemia. Transient normalization of the marrow and blood.] Sang 18 (8): 474-480, 1947.

Fairburn, E. A., & Burgen, A. S. V. [Middlesex Hosp., London, Eng.]: The skin lesions of monocytic leukaemia. Brit. J. Cancer 1: 352-362, Dec., 1947.—Case report.

Frangella, Alphonso [Inst. Radiol. et Sc. physiques, Montevideo, Uruguay]: Traitement de certaines affections tumorales par le radon intraveineux. Technique, indications thérapeutiques, essai de comparaison avec les isotopes radioactifs. [Treatment of certain tumors by intravenous radon. Technique, therapeutic indications, attempt to compare with radioactive isotopes.] Paris méd. 38: 146-151, Mar. 20, 1948.—Leukemia, lymphogranulomatosis and other reticulo-endothelial diseases, bony metastases, and toxic goiter are discussed particularly.—*M. C. J.*

Freeh, Henry C. [Savannah, Ga.]: Chronic lymphatic leukemia occurring simultaneously in brothers. J. M. A. Georgia 37: 183-184, May, 1948.—Case report of brothers 59 and 52 yrs. of age.

Gauld, W. R. [Aberdeen Roy. Infirmary, Scotland]: Leukaemia presenting with neurological manifestations. Lancet 1: 939-941, June 19, 1948.—Three case reports.

Giraud, G.; Cazal, P., & Bertrand, L.: Insuccès de l'uréthane dans deux cas de leucémie chronique. [Failure of urethane in two cases of chronic leukemia.] Montpellier méd. 31/32: 385-386, Nov./Dec., 1947.

Gross, Ludwik, & Matte, Michael L. [Veterans Adm. Hosp., New York City]: The occurrence of tumors and leukemia in members of families of patients suffering from leukemia. New York State J. Med. 48: 1283-1284, June 1, 1948.

Guichard, A., & Cortet, P.: Deux cas de leucémie aiguë a début intestinal et péritonéal, pseudo-appendiculaire. [Two cases of acute leukemia, the onset showing intestinal and peritoneal symptoms simulating appendicitis.] Lyon méd. 178: 601-604, Sept. 14, 1947.

Hanoune, S.: Un cas de vertèbre d'ivoire au cours de la maladie de Hodgkin. [A case of ivory vertebra in Hodgkin's disease.] J. de radiol. et d'électrol. 28 (9/10): 423-424, 1947.

Janbon, M.; Chaptal, J.; Cazal, P., & Bertrand, L. [Montpellier, France]: Réticulose leucémique (leucémie à monocytes type Schilling) et tuberculose gangliopulmonaire. [Leukemic reticulosis (Schilling-type monocytic leuke-

mia) and tuberculosis of the pulmonary lymph nodes.] Sang 18 (9): 535-544, 1947.

Leblond, Sylvio; Tremblay, L., & Dunne, Roger [Hôp. Anciens Combattants, Que.]: A propos d'un cas de leucémie myéloïde aleucémique. [A case of aleukemic myeloid leukemia.] Laval méd. 13: 187-200, Feb., 1948.—Detailed case report.

Lorenz, W. [Marburg, Germany]: Über einen malignen Tumor des lymphopoetischen Gewebes mit aussergewöhnlicher Strahlenempfindlichkeit. [A malignant tumor of the lymphopoietic tissue extraordinarily sensitive to irradiation.] Strahlentherapie 77 (1): 33-38, 1947.—The author described the tumor as a sarcoma of the lymphoblastic tissue independent of the lymph system that was immature and hence very radiosensitive.—*M. C. J.*

Marchal, Georges: L'anémie de la maladie de Hodgkin. [The anemia of Hodgkin's disease.] Rev. d'hémat. 2 (4): 479-497, 1947.

Marionone, Giuseppe: Sur la solubilité des granulations des mastzellen dans les leucémies myéloïdes. [The solubility of mast-cell granulations in myeloid leukemia.] Sang 18 (7): 405-406, 1947.

Nelson, W. O. B., & Dwinnell, L. A. [Fergus Falls Clin., Fergus Falls, Minn.]: Abdominal Hodgkin's disease. With report of a case involving retroperitoneal nodes. Minnesota Med. 31: 647-650, June, 1948.

Paolino, Walter, & De Sario, Pier Nicola [Univ. Turin, Italy]: Studio comparativo dell'azione sui globuli bianchi del metiltiouracile e dell'aminotiazolo nei soggetti leucemici e non leucemici. [Comparative study of the action of methylthiouracil and aminothiazole on the leukocytes in leukemics and nonleukemics.] Minerva med. 2: 488-494, Dec. 8, 1947.

Ravault, P., & Guinet, P.: Les lymphadénies aleucémiques atypiques avec éosinophilie. A propos de certaines modalités évolutives (régression ou passage à la lymphosarcomatose). [Atypical aleukemic lymphadenopathies with eosinophilia. Certain developmental potentialities (regression or transition into lymphosarcomatosis).] Sang 18 (8): 453-465, 1947.

Ravault P., & Guinet, P.: Sur certaines modalités évolutives des lymphadénies aleucémiques avec éosinophilie. Les formes évoluant vers le lymphosarcome. Les formes régressives. [Certain developmental potentialities in aleukemic lymphadenitis with eosinophilia. Forms developing toward lymphosarcoma; regressive forms.] Lyon méd. 178: 769-775, Nov. 23, 1947.

Ravault, P.; Roche, L., & Confavreux, J.: Cryptoleucémie aiguë consécutive à un traitement par radiothérapie et thorium X au cours d'une spondylose rhizomélique. [Acute cryptoleukemia following x-ray and thorium X treatments for a rhizomelic spondylosis.] Lyon méd. 179: 21-23, Jan. 11, 1948.—Case report.

Raynaud, Robert; Imbert, Charles, & Eslongues, Jean Robert, d' [Algiers, Algeria]: Hémopathie benzolique avec myéloblastose intense sans manifestations cliniques. [Benzol hemopathy with intense myeloblastosis, without clinical symptoms.] Sang 18 (7): 418-420, 1947.

Rimbaud, L.; Serre, H.; Vedel, A., & Boyer, F.: Maladie de Hodgkin à détermination pulmonaire prédominante. Intérêt des tomographies en série. [Hodgkin's disease, predominantly pulmonary in location. Value of serial tomography.] Montpellier méd. 31/32: 312, Sept./Oct., 1947.

Rossi, C.: Diabete insipido da linfogranuloma maligno. [Diabetes insipidus lymphogranulomatosis.] *Riv. clin. med. 47 (8/10): 565,* 1947.—Case report.

Röttjer, Ernesto A., & Lascalea, Miguel C.: El "gas mostaza" en el tratamiento de la enfermedad de Hodking. [Mustard gas in the treatment of Hodgkin's disease.] Rev. san. mil. argent. 46: 599-601, Oct./Dec., 1947.—A review.

Röttjer, Ernesto A.; Lascalea, Miguel C., & Latienda, Ramón L.: Reticulosarcoma primitivo de bazo. [Primary reticulosarcoma of the spleen.] Rev. san. mil. argent. 46: 549-556, Oct./Dec., 1947.—Case report.

Röttjer, Ernesto A.; Lascalea, Miguel C.; Latienda, Ramón J., & Rodrigo, Alberto R.: Reticulosarcoma primitivo del bazo. [Primary reticulosarcoma of the spleen.] Rev. Asoc. méd. argent. 62: 18-22, Jan. 15-30, 1948.—Case report.

Schwertman, Arthur J. [Covington, Ky.]: Anemia of malignancy. South. M. J. 41: 598-601, July, 1948.—Discussion of anemia in 58 cases of carcinoma in 8 different organs.

Storti, Edoardo, & Mauri, Carlo [Univ. Pavia, Italy]: L'etiluretano nella terapia delle leucemie. (Contributo clinico-ematologico.) [Ethyl-urethane in treatment of leukemia. (Clinicohematological study.)] Minerva med. 2: 440-448, Nov. 24, 1947.—Based on 9 cases of chronic myeloid leukemia, 4 of chronic lymphadenosis, and 2 of acute leukemia.

Summers, John E., & Reid, Wells C. [Goodrich Gen. Hosp., Goodrich, Mich.]: Hodgkin's disease complicated by pregnancy. J. A. M. A. 137: 787, June 26, 1948.—Case report.

Tedeschi, C. G., & Carnicelli, T. J. [Framingham Union Hosp., Mass.]: Manifold manifestations of reticuloendothelial disease. Report of a case of Hodgkin's disease (lymphogranulomatosis), acute hemolytic anemia and giant follicular lymphadenopathy. Arch. Path. 45: 171-178, Feb., 1948.

Van der Meiren, L. [St. Peter's Hosp., Brussels, Belg.]: Three cases of Hodgkin's disease with

predominantly cutaneous localization. Brit. J. Dermat. 60: 181-184, May, 1948.

Warren, Shields [Harvard M. Sch., Boston, Mass.]: Tumor Seminar. [A] ? Hodgkin's disease of an axillary lymph node: ? fibrosarcoma involving an axillary lymph node. [B] Plasma cell leukemia. J. Missouri State M. A. 45: 355-356; 356-360, May, 1948.

MUSCULOCUTANEOUS SYSTEM

Gullino, Piero [Univ. Torino, Italy]: Sui sarcomi derivati dal rivestimento sinoviale delle guaine tendinee, delle articolazioni, delle borse mucose. [Sarcoma derived from the synovial lining of the tendon sheaths, the joints, and the bursa mucosa.] Tumori 21 (4/5): 229-263, 1947.—A study of 13 cases.

Hatcher, C. Howard: Extra skeletal ossification simulating sarcoma. Proc. Inst. Med. Chicago 17: 122, May 15, 1948.

Hobbs, M. E. [Millbrook, Ont.]: Rhabdomyosarcoma. Canadian M. A. J. 59: 65-66, July, 1948.—Case report.

Jenkins, H. B. [Donalsonville, Ga.]: Xanthomatous tumors of the Achilles tendon. J. M. A. Georgia 37: 176-178, May, 1948.—Case report.

Marinello Vidaurreta, Zoilo: El sarcoma del tejido de granulación. [Sarcoma of granulation tissue.] Rev. méd. cubana 59: 11-18, Jan., 1948.—A review.

Stout, Arthur Purdy [Columbia Univ., Coll. Phys. & Surgeons, New York City]: Fibrosarcoma. The malignant tumor of fibroblasts. Cancer 1: 30-63, May, 1948.

Stout, Arthur Purdy [Columbia Univ., Coll. Phys. & Surgeons, New York City]: Myxoma, the tumor of primitive mesenchyme. Ann. Surg. 127: 706-719, Apr., 1948.—"Myxoma" is defined as a true neoplasm, composed of stellate cells set in a loose mucoid stroma through which course very delicate reticulin fibers in various directions, and closely resembles primitive mesenchyme. There may be some variation in density and fibrosis, but there must be no chondroblasts, lipoblasts, rhabdomyoblasts, or other recognizable differentiated elements. Tumors such as liposarcoma, fibrosarcoma, chondrosarcoma containing myxoid elements should not be considered as variants of the myxoma with "myxo-" included in the name, since they behave clinically like tumors composed of the dominant tissue. The term myxosarcoma should not be used since myxomas do not metastasize and there is no way to anticipate differences in their growth energy from their histopathology. More than 100 cases of myxoma involving the heart have been reported, but since these are the only tumors given that name from which metastases have been described, the suspicion is warranted that such metastasizing tumors are probably not true myxomas but sarcomas of some other type masquerading as myxoma.

The available literature includes 95 recorded cases of myxoma, exclusive of the heart, and the author has recognized 49 cases in his own material. It is found equally in both sexes at all ages and in many tissues, but most frequently in the heart, the skin and soft parts, and bones; the genitourinary cases develop in the bladder. Soft-part myxomas have no striking clinical characteristics. The duration of symptoms (i.e., tumor) before treatment varied from 2 wks. to 37 yrs. (av. 4 yrs.). Myxomas tend to grow very slowly or remain stationary for long periods of time and then may suddenly enlarge rapidly. Rapid growth may come at the beginning or end of a quiescent period.

Surgical excision has been the most common treatment. Radiation therapy has generally been either entirely or partly unsuccessful. Since the tumor infiltrates, close excision has frequently been followed by recurrence. With most myxomas it is usually necessary to remove a generous amount of apparently uninvolved surrounding tissue to effect eradication. The possibility of metastases need not be considered in treatment, but recurrence in some region where vital structures can be affected, such as the bladder and retroperitoneal region, may result in death. Of the 27 followed cases in the author's material, 14 were alive without tumor, 10 were alive with tumor, 1 died following operation, 1 died because of tumor, and 1 of intercurrent disease with tumor persisting.—*A. G. Foraker, M.D.*

Warren, Shields [Harvard M. Sch., Boston, Mass.]: Tumor Seminar. [A] Synovial sarcoma of the soft tissue of the leg. [B] Desmoid of the abdominal wall. [C] ? Benign giant cell tumor of tendon sheath. J. Missouri State M. A. 45: 351-354; 354-355; 383-384, May, 1948.

SKIN

Anon.: Melanoma. Mississippi Doctor 25: 389-391, May, 1948.

Arnold, Harry L., Jr. [The Clinic, Honolulu, Hawaii]: Malignant melanoma of the skin: its origin, recognition, prevention and management. Proc. Staff Meet. Clin., Honolulu 14: 1-4, Jan., 1948.

Austin, E. R. [The Clinic, Honolulu, Hawaii]: Malignant melanoma of the skin. Report of four-year "cure" by radical surgical excision. Proc. Staff Meet. Clin., Honolulu 14: 11-13, Mar., 1948.

Bernier, Joseph L., & Clark, Mardelle [Army Inst. Path., Washington, D. C.]: Carcinoma of the lip. Preliminary analysis of 330 cases with follow-up of from 3 to 36 years. Mil. Surgeon 102: 474-479, June, 1948.

Capdevila, J.: Lesiones cutáneas precepitelioma-tosas. [Pre-epitheliomatous cutaneous lesions.] Prensa méd. argent. 35: 251-254, Feb. 6, 1948.

Cintract, J. Maurice [Hôp. Montfermeil, France]: Tumeur mélanique sous-unguéale. [Subungual melanotic tumor.] Presse méd. 56: 247-248, Mar. 31, 1948.—Case report; tumor recurred after excision.—*M. C. J.*

Crozet: Trois épithéliomas primitifs de structure à peu près semblable chez un même sujet. [Three primary epitheliomas of somewhat the same structure in the same patient.] Rev. de laryng. 68: 540-542, Sept./Oct., 1947. —The epitheliomas, in a man of 71 yrs., were located on the right ear, the lower right eyelid, and the right leg. The pathological diagnoses were: poorly differentiated squamous carcinoma, tending to spindle-cell; poorly differentiated squamous carcinoma; basal-cell epithelioma.—*M. C. J.*

Curth, Helen Ollendorff [New York City]: **Acanthosis nigricans and its association with cancer.** Arch. Dermat. & Syph. 57: 158-170, Feb., 1948.

Davis, Albert D., & Berner, Robert E. [Stanford Univ. Sch. Med., San Francisco, Calif.]: **Dermoid cysts of the nose.** Plast. & Reconstruct. Surg. 3: 345-351, May, 1948.—Three case reports.

Degos, R. [Hôp. Saint-Louis, Paris, France]: **Le traitement des cancers de la peau. [Treatment of skin cancers.]** Paris méd. 38: 55-60, Jan. 24, 1948.—A review.

Grace, Arthur W. [Long Island Coll. Med., Brooklyn, New York City]: **Hemangiomas of the skin and their treatment.** M. Times, New York 76: 188-193, May, 1948.

Gutiérrez García, David, & Diez de Urdanivia, Agustín [Inst. Radium Habana, Cuba]: **Enfermedad de Bowen. [Bowen's disease.]** Arch. cubanos cancerol. 6: 266-272, July/Sept., 1947. —Two case reports.

Helmke, Roderich [Jena, Germany]: **Uber den Mitosenrhythmus bei Karzinomen der menschlichen Haut unter dem Einfluss der Chaoulschen Nahbestrahlung. [Mitotic rhythm in carcinoma of human skin after Chaoul contact irradiation.]** Strahlentherapie 77 (2): 259-264, 1947.—Thirteen basal-cell epitheliomas were given 500 r and 13 prickle-cell carcinomas 500 r or 3000 r Chaoul irradiation and the skin examined 3, 6, 9, 12, 24, 28, 34, and 48 hrs. later. Most of the carcinomas showed an initial rise, a primary effect, a mitosis-poor intermediate period, and a secondary effect. In most respects the results confirmed those of Jüngling and Langendorff who used greater STD's.—*M. C. J.*

Jausion, H.; Cailliau, F., & Calop, R. [Paris, France]: **Maladie de Kaposi et sarcomatose éruptive. [Kaposi's disease and eruptive sarcomatosis.]** Presse méd. 56: 240-241, Mar. 31, 1948.

Laycock, H. T.: The "kang cancer" of northwest China. Brit. M. J. 1: 982, May 22, 1948. —Notation of 6 cases with brief description of 1.

Pulvermacher, Else [Univ. Marburg, Germany]: **Krebsentstehung als Folge einer Kriegsverletzung. [Cancer resulting from a war injury.]** Med. Klin. 42: 857-858, Dec., 1947.—Case report: The patient received an abdominal wound 10-15 cm. long that suppurated for 8 wks.; 17 mos. later, thickening appeared in scar; another yr. later, a highly differentiated, fibroblastic sarcoma of the cutis and subcutis, which had infiltrated neighboring areas and subcutaneous fat, was found.—*M. C. J.*

Straith, Claire L. [Harper Hosp., Detroit, Mich.]: **Plastic surgery in facial cancer.** Plast. & *Reconstruct. Surg. 3: 262-268, May, 1948.*—Two case reports.

NERVOUS SYSTEM

DeVoe, Robert W.; Lovelady, Sim B.; Dockerty, Malcolm B., & Gray, Howard K. [Mayo Clin., Rochester, Minn.]: **Pregnancy complicated by presacral neurofibroma, one of the so-called Middeldorpf tumors: report of case.** Proc. Staff Meet., Mayo Clin. 23: 239-244, May 12, 1948.

Fincher, Edgar F., & Swanson, Homer S. [Emory Univ. Sch. Med., Ga.]: **Spinal cord tumors and the similarity of their symptoms to those of other more common diseases.** South. Surgeon 14: 111-123, Feb., 1948.—Of 50 cases of microscopically proved intradural tumors of the spinal cord, 37 (74%) were histologically benign: arachnoid cyst, 1; dermoid cyst, 1; glioma, 12 (astrocytoma, 5; ependymoma, 5; unclassified, 2); hemangioma, 2; Hodgkin's disease (primary), 1; lipoma, 1; meningioma, 10; neurofibroma, 22. 18 (36%) *had been mistakenly subjected to general surgical* procedures before the correct diagnosis was made. Pain, consistent in location and character, is the dominating symptom. 9 cases are presented in detail and the relevant clinical problems discussed.—*D.A.S.*

Harvey, W. F. [Roy. Coll. Phys., Edinburgh, Scotland]: **Argument on neural tumours and their allies.** Edinburgh M. J. 55: 1-16, Jan., 1948.

Kimbrough, James C.; Furst, John N., & Worgan, David K. [Walter Reed Gen. Hosp., Washington, D. C.]: **Multiple neurofibromatosis involving the urinary bladder.** Mil. Surgeon 102: 346-347, May, 1948.—Case report.

Paillas, Jean; Gastaut, H.; Tamalet, J., & Verspick [Marseille, France]: **Intérêt de l'électroencéphalographie pour le diagnostic et la localisation des tumeurs cérébrales. Remarques sur la valeur comparée des données cliniques, ventriculographiques et électriques. [Electroencephalography in the diagnosis and localization of cerebral tumors. Remarks *on the comparative value of clinical findings*, ventriculograms, and the electroencephalogram.]** Rev. neurol. 79: 688-692, Oct./Nov., 1947.

Samson, Mathieu, & Patry, Laurent [Hôp. Saint-Michel-Archange, Que.]: **Maladie de Recklinghausen. (Présentation de malade et observation anatomo-clinique.) [von Recklinghausen's disease. (Presentation of a patient and anatomicoclinical report.)]** Laval méd. 13: 37-47, Jan., 1948.

BRAIN AND MENINGES

Bassett, Robert C., & Bagchi, Basu K. [Univ. Michigan M. Sch. & Hosp., Ann Arbor]: Intracranial neoplasm localized electroencephalographically by the use of a three-dimensional scheme. J. Neurosurg. 5: 298-306, May, 1948. —A case of a left parasagittal premotor meningioma, weighing 120 gm. precisely, localized by electroencephalographic methods, and its presence confirmed at operation without the utilization of other diagnostic aids, has been reported.—*Auth. Summ.*

Bronfman, S., & Reumont, M.: La sarcomatose méningée primitive. (Etude clinique et histopathologique.) [Primary meningeal sarcomatosis. (Clinical and histopathological study.)] J. belge de neurol. et de psychiat. 47: 729-757, Dec., 1947.—Three case reports and review of all cases in the literature.

Cardona, Filippo [Univ. Florence, Italy]: Sulla scarsa importanza della ipertensione endocranica nella produzione dei disturbi psichici in tumori cerebrali. [Importance of endocranial hypertension in mental disturbances in cases of brain tumor.] Rassegna di studi psichiat. 36: 650-657, Oct./Dec., 1947.—On the basis of 50 brain tumors, the author concludes the endocranial hypertension has little effect in inducing mental disturbances.—*M. C. J.*

Dublin, William B. [Indianapolis City Hosp., Ind.], & Brown, Robert W.: Paraphysial cyst of third ventricle. Northwest Med. 47: 427-430, June, 1948.—Case report.

Hesser, Frederick H. [Duke Univ. Sch. Med., Durham, N. C.]: Clinical manifestations of glioblastoma multiforme. A review of fifty cases. North Carolina M. J. 9: 179-186, Apr., 1948.

Kaplan, Abraham [Mt. Sinai Hosp., New York City]: Pia-arachnoidal cysts of the posterior fossa. Am. J. Surg. 76: 102-106, July, 1948.—Two case reports.

Moore, George E. [Univ. Minnesota M. Sch., Minneapolis]: Use of radioactive diiodofluorescein in the diagnosis and localization of brain tumors. Science 107: 569-571, May 28, 1948.—Sodium diiodofluorescein was synthesized to contain I^{121} in an amount necessary to give 1 mc. of radioactivity/10 cc. of a 2% solution of the final product. An amount of dye calculated to contain 500-600 μc. of radioactivity was injected intravenously in 12 cases with a suspected brain tumor. Counts were taken with a Geiger-Müller tube at 3- to 5-min. intervals at each of several positions on the skull with the detection cone directly on the skin. Although counting was begun soon after the dye was injected, differential readings between areas over the suspected tumor and symmetrical control areas were not found before 2-4 hrs. Conclusions as to the presence or absence and localization of tumor were confirmed by operative findings in 11 cases. In the other, no significant counts were obtained, although an acoustic neuroma was found at operation. 3 previous cases, with known site of recurrence following previous partial operative excision, were also studied.—*D. A. S.*

Ortiz de Zárate, Julio C., & Insausti, Tomás: Sarcomatosis meningea difusa primitiva. [Primary diffuse meningeal sarcomatosis.] Rev. Asoc. méd. argent. 61: 795-798, Nov. 15, 1947.—Case report.

Quade, R. H. [Neenah, Wis.]: Practical aspects of diagnosing brain tumors. Wisconsin M. J. 47: 583-586, June, 1948.

Ruckensteiner, E. [Univ. Innsbruck, Austria]: Über Kalkhüllen an Meningeomen. [Calcareous envelopes of meningiomas.] Krebsarzt 3: 161-168, May, 1948.—Two case reports in which x-rays showed a calcareous lining of meningiomas of the orbit and of the posterior cranial cavity.

Russell, Dorothy S.; Marshall, A. H. E., & Smith, F. B. [London Hosp., Eng.]: Microgliomatosis. A form of reticulosis affecting the brain. Brain 71: 1-15, Mar., 1948.—A series of 7 cases of cerebral tumor is described in which the proliferating cells are predominantly of the microglial type. In 3 cases the cerebral tumors were associated with lesions of similar histology in other organs. It is considered that the character of the lesions in the brain and other organs justifies the classification of the condition as a reticulosis. The relation of these cases to similar examples in the literature is discussed.—*Auth. Summ.*

Stenhouse, David [Killearn Hosp., Stirlingshire, Scotland]: Plain radiography of the skull in the diagnosis of intracranial tumours. Brit. J. Radiol. 21: 287-300, June, 1948.—An analysis was made of the plain radiographic findings in 200 verified cases of intracranial tumor. Sellar changes were found in 2 groups of lesions: tumors in or near the sella, and tumors at a distance from it (metasellar lesions). Of all the abnormal sellar appearances, only 2 were considered to be of localizing value: uniform expansion with little or no thinning of dorsum, and suprasellar calcification. The commonest changes were thinning or erosion of dorsum, and these were common to both groups of lesions. In metasellar lesions showing sellar changes, the degree of sellar destruction and the degree of hydrocephalus are roughly proportionate to one another, but the hydrocephalus in itself is not the cause of the bone destruction. In some of these cases, however, the dilated anterior end of the third ventricle comes into close contact with the sella, and it is suggested that this may be at least a contributory cause of the sellar changes. Signs of increased intracranial tension, comprising the starting of sutures, increased convolutional markings, widening of the occipital emissary foramina, and thinning or erosion of the dorsum sellae, were found in 22.5% of all cases. Localizing signs were found in 30.5%. They included pineal shift, calcification, bone erosion, new bone formation, and

widening of the vascular channels.—*Auth. Summ.*

Torkildsen, Arne [Neurolog. & Neurosurg. Univ. Clin., Oslo, Norway]: **Should extirpation be attempted in cases of neoplasm in or near the third ventricle of the brain? Experiences with a palliative method.** J. Neurosurg. 5: 249-275, May, 1948.—In view of the unsatisfactory results with attempts at surgical removal of neoplasms in or near the third ventricle, the author suggests a new palliative operative procedure—ventriculocisternostomy—that establishes an artificial communication between the lateral ventricle and the cisterna magna, thus relieving the hydrodynamic alterations caused by the obstruction of flow of the cerebrospinal fluid. By means of a rubber tube running outside the cranium, with one end in the lateral ventricle and the other end fixed in the cisterna magna, the cerebrospinal fluid is short-circuited about the pathological region. Ventriculocisternostomy was performed in 8 cases for tumor in the pineal region, with 1 postoperative death, and in 11 cases for tumor in or near the third ventricle outside the pineal region, with 2 fatalities.

Symptoms, signs, pathological findings, and results are discussed in detail. The author concludes that the fate of the patients depends primarily on the malignant nature of the neoplasm, but since most of the tumors are of very slow growth, the patients may live comfortably if the symptoms due to the obstruction of the flow of cerebrospinal fluid can be relieved.—*F. S. Butler, M.D.*

EYE

Bischler, V. [Geneva, Swtz.]: **Un cas de kyste congénital scléro-cornéen.** [A congenital sclerocorneal cyst.] Ophthalmologica 114: 371-376, Oct./Nov., 1947.

King, E. F.: Retinal glioma, with successful use of radon seeds. Proc. Roy. Soc. Med. 41: 268, May, 1948.—Two case reports.

Radnót, Magda [II. Univ.-Augenklin., Budapest, Hungary]: **Uber das flache Sarkom der Aderhaut.** [Surface sarcoma of the choroid.] Ophthalmologica 114: 409-414, Dec., 1947.—One case of highly pigmented polymorphous-cell sarcoma, 1 of spindle-cell sarcoma.

Sachs, Erich [Chicago, Ill.], **& Larsen, Reuben L.: Cancer and the lens.** Am. J. Ophth. 31: 561-564, May, 1948.—Factors of biologic, metabolic, physical, and chemical nature—any or all of which may be responsible for the nonexistence of cancer in the lens—are considered and discussed.—*Auth. Summ.*

Sien, Auw-Yang [Amsterdam Univ., Neth.]: **A case of choroidal apoplexy diagnosed as a sarcoma of the choroid.** Ophthalmologica 115: 1-10, Jan., 1948.

Swan, Kenneth C.; Emmens, Thomas H., & Christensen, Leonard [Univ. Oregon M. Sch., Portland]: **Experiences with tumors of the limbus.** Tr. Am. Acad. Ophth. [1948]: 458-469, May/June, 1948.

OSSEOUS SYSTEM

Brailsford, James F. [Roy. Cripples Hosp., Birmingham, Eng.] **Ossifying haematomata and other simple lesions mistaken for sarcomata. The responsibility of biopsy.** Brit. J. Radiol. 21: 157-170, Apr., 1948.

Cahan, William G.; Woodard, Helen Q.; Higinbotham, Norman L.; Stewart, Fred W., & Coley, Bradley L. [Memorial Hosp., New York City]: **Sarcoma arising in irradiated bone. Report of eleven cases.** Cancer 1: 3-29, May, 1948.

Chesterman, Judson T. [Sheffield, Eng.]: **Solitary plasmocytoma of the long bones.** Brit. J. Surg. 35: 440, Apr., 1948.—Follow-up report on 4 cases surviving 4, 8, 9, and 12 yrs.

Gavaudan; Causse, & Gros, Cl.: Méningiome de l'arête avec volumineux ostéome du sphénoïde. [Meningioma of the spinous process *of the sphenoid with large osteoma of the* sphenoid.] Montpellier méd. 31/32: 318-319, Sept./Oct., 1947.—Case report.

Góes, Henrique, de: Osteoma osteóide. [Osteoid osteoma.] Rev. brasil. de cir. 17: 89-96, Feb., 1948.—A review.

Guillaumont, B., & Guiot, G.: La radiologie des cranio-pharyngiomes kystiques. [Radiology of cystic craniopharyngiomas.] J. de radiol. et d'électrol. 28 (9/10): 422-423, 1947.—Preliminary report.

Hauser, Emil D. W., & Constant, George A. [Northwestern Univ. M. Sch., Chicago, Ill.]: **Skeletal hemangio-endothelioma. A case report.** J. Bone & Joint Surg. 30-A: 517-521, Apr., 1948.—Involvement of both hips, believed by the authors to be two primary lesions.

Huerta, F. R., de la: Mieloma múltiple. Reporte de un caso con serología hiperpositiva. [Multiple myelomas. Report of a case with supernormal serology.] Rev. méd. cubana 59: 1-6, Jan., 1948.

Kent, Edward M., & Ashburn, F. S. [M. C., U. S. Nav. M. Center, Bethesda, Md.]: **Ewing sarcoma of the rib.** Am. J. Surg. 75: 845-848, June, 1948.—Case report.

Kolff, W. J., & Dhont, J. [Municipal Hosp. "Engelenberg" Found., Kampen, Neth.]: **Plasmocytoma (multiple myelomas, Kahler's disease), and its attendant disturbances in the protein metabolism.** Am. J. M. Sc. 215: 405-410, Apr., 1948.

Köves, Stephan [Ungarisch. Peter-Pázmány-Univ., Budapest, Hungary]: **Primäres Ewing-Sarkom der Wirbelsäule.** [Primary Ewing sarcoma of the spine.] Schweiz. med. Wchnschr. 78: 380-383, Apr. 24, 1948.

Lapeyre; Romieu; Campo, & Bringer: Maladie de Paget et sarcome. [Paget's disease and sarcoma.] Montpellier méd. 31/32: 359-360, Nov./Dec., 1947.—Case report.

Leger, Henry [Bordeaux, France]: **Les myélomes. Etude histo-biologique.** [Histobiological study

of myelomas.] Presse méd. 56: 236-237, Mar. 31, 1948.

Limonzi, M. [Orléans, France]: Dégénérescence maligne d'une exostose ostéogénique. [Malignant degeneration of an osteogenic exostosis.] J. de radiol. et d'électrol. 28 (9/10): 401-402, 1947.—Case report.

Misra, S. C.: Sharma, M. L., & Singh, Jaswant [M. Coll., Agra, India]: Osteoid osteoma. Indian J. Surg. 9: 198-201, Dec., 1947.—Case report.

Natale, A., & Freidemberg, Jorge [Rosario, Argentina]: Sarcoma del maxilar superior. [Sarcoma of the superior maxilla.] Rev. méd. de Rosario 38: 30-36, Jan., 1948.—Case report.

Pritchard, J. E., & McKay, J. W. [McGill Univ. & Montreal Gen. Hosp., Que.]: Osteoid osteoma. Canadian M. A. J. 58: 567-575, June, 1948.—Report of 15 cases.

Ravault, P.: Vignon, G.; Gallet, J.; Berthier, L., & Schott, B.: La néphrite azotémique du myélome multiple. (A propos d'une nouvelle observation.) [The azotemic nephritis of multiple myeloma. (A further case.)] Lyon méd. 178: 665-668, Oct. 12, 1947.

Rubinstein, Michael A. [Montefiore Hosp., New York City]: Aspiration of bone marrow from the iliac crest. Some technical and diagnostic advantages versus sternal aspiration. Bull. New York Acad. Med. 24: 400-401, June, 1948.

Serret, J.: Sarcome ostéogénique ou ostéopériostite simulant un sarcome. [Osteogenic sarcoma or osteoperiostitis simulating a sarcoma.] J. de radiol. et d'électrol. 28 (9/10): 432-434, 1947.—Case report.

Shackman, Ralph, & Harrison, C. V. [Brit. Post Grad. M. Sch., London, Eng.]: Occult bone metastases. Brit. J. Surg. 35: 385-389, Apr., 1948.

Sherman, Robert S. [Memorial Hosp., New York City], & Sternbergh, Waldemar C. A.: The roentgen appearance of ossifying fibroma of bone. Radiology 50: 595-609, May, 1948.—Twelve cases of ossifying fibroma of bone have been studied, primarily from the point of view of x-ray diagnosis. 6 involved the maxilla, 5 the mandible, and 1 the temporal bone. The clinical and x-ray features are believed to be sufficiently distinct to warrant acceptance of ossifying fibroma as a separate entity. The x-ray findings are usually suggestive of the diagnosis and in certain instances may be characteristic. The picture is that of a unilocular lesion, in most cases limited to the maxilla or mandible, oval to spherical in shape, with a distinct boundary, usually of an egg-shell character. In the lower jaw, the origin is from the medullary portion of the bone; in the upper jaw, the tumor arises similarly or subperiosteally. In its early phase the process is predominantly osteolytic, with little or no internal architecture, and no periosteal reaction. Enlargement is progressive, with an increased productive element brought about in the maxilla by the formation of spherical densities and in the mandible by irregular striae. A unique growth change in the maxilla is the dissolution of adjacent bone without pressure displacement. A brief discussion of clinical, pathological, and treatment aspects, particularly as they bear on x-ray diagnosis, has been included. —*Auth. Summ.*

Snapper, I. [New York City]: Treatment of multiple myeloma with "stilbamidine." Clinical results and morphologic changes. J. A. M. A. 137: 513-516, June 5, 1948.—In 80% of the cases of multiple myeloma, the pains are at least partly relieved by intravenous or intramuscular injections of "stilbamidine" (4,4'-stilbenedicarboxamidine). The disease is at best halted temporarily; relapses are frequent, and Bence Jones proteinuria and increase of globulin in the serum are not influenced. The drug should be handled with care in patients who have impaired renal function, as is frequently the case in Bence Jones proteinuria. The drug has no deleterious influence either on hepatic function or on the peripheral blood picture. In the majority of the cases a dissociated anesthesia of the trigeminal branches sets in several months after the termination of treatment. This anesthesia does not lead to dangerous complications, although occasionally disagreeable subjective complaints of itching of the eyes have occurred. After treatment with "stilbamidine," a specific alteration of the cytoplasm of the myeloma cells is observed, consisting of the formation of precipitates of ribonucleic acid conjugated with "stilbamidine." It is probable that the nucleoproteins of the cytoplasm of the myeloma cells are different from the nucleoproteins of any other cells in the body. "Stilbamidine" evidently has a specific affinity for these abnormal nucleoproteins of the myeloma cells.—*Auth. Summ.*

Spitzer, Richard, & Price, L. Woodhouse [West End Hosp. Nervous Dis., London, Eng.]: Solitary myeloma of the mandible. Brit. M. J. 1: 1027-1028, May 29, 1948.—Case report.

Stevenson, Harwood [Roy. Nat. Orthopaedic Hosp., Stanmore, Eng.]: Multiple myelomatosis. A clinico-pathological review, with a report of a case of myeloblastic type. Post Grad. M. J. 24: 269-282, May, 1948.

Warren, Shields [Harvard M. Sch., Boston, Mass.]: Tumor Seminar. [A] Paget's disease of the skull with osteogenic sarcoma. [B] Adamantinoma of the tibia. J. Missouri State M. A. 45: 348-349; 349-351, May, 1948.

Weismann-Netter, R.; Robert-Lévy, J., & Gabe, M.: A propos d'un cas de myélome atypique. [A case of atypical myeloma.] Sang 18 (7): 428-433, 1947.

Wuhrmann, F.; Wunderly, Ch., & Wiedemann, E. [Univ.-Klin. Zürich, Swtz.]: Ueber das Alpha-Globulin-Plasmocytom. [Alpha-globulin plasmocytoma.]. Schweiz. med. Wchnschr. 78: 180-182, Feb. 28, 1948.—The author suggests this is another subtype of multiple myeloma (Kahler's disease).

RESPIRATORY TRACT

NOSE : SINUSES : PHARYNX

Greenfield, Maurice M. [Walter Reed Gen. Hosp., Washington, D. C.]: **Malignant plasmocytoma of the nasopharynx. A case of multiple myeloma primary in the nasopharynx.** Radiology 50: 661-665, May, 1948.—Metastasis to regional lymph nodes and distant multiple osseous involvement.

Hétroy, Michel [Amiens, France]: **Un cas de fibrome naso-pharyngien.** [**A case of nasopharyngeal fibroma.**] Rev. de laryng. 68: 543-544, Sept./Oct., 1947.

Laffargue, Bernard [Univ. Bordeaux, France]: **Considérations sur les fibromes naso-pharyngiens. Etude anatomo-clinique.** [**Nasopharyngeal fibromas. Anatomicoclinical study.**] Rev. de laryng. 68: 436-465; 514-539, Aug.; Sept./Oct., 1947.—A review.

Passe, E. R. Garnett [London, Eng.]: **Primary carcinoma of the eustachian tube.** J. Laryng. & Otol. 62: 314-315, May, 1948.—Case report: squamous carcinoma.

Rius, F. Ciscar [Cátedra Histol. y Anat. Patol., Barcelona, Spain]: **Tres casos de retículo-sarcomas cordonales faringeos (tumores linfo-epiteliales de Schmincke).** [**Three cases of reticulosarcoma of the pharyngeal ring (Schmincke's lympho-epithelioma).**] Med. clín., Barcelona 9: 219-223, Oct., 1947.

Tod, Margaret C. [Christie Hosp., Manchester, Eng.]: **The treatment of cancer of the maxillary antrum by radium.** Brit. J. Radiol. 21: 270-275, June, 1948.—Of 222 cases of antrum cancer treated between 1932-1941, 100 were handled during the 2d 5-yr. period by the simple method of inserting the radium source into the center of the tumor through a Caldwell-Luc or palatal defect. The radium was calculated to deliver 8000 to 10,000 r at 2 cm., the estimated surface of the tumor, over a period of 7 to 10 days. Surgery for drainage was used as indicated. The method was not used for mixed salivary-gland tumors or for lymphosarcoma. Although the author implies that better end results were obtained by this method of treatment, the comparative tables of 5-yr. results are approximately the same—25% in 222 cases treated by all methods, and 26% in 100 cases handled by the more recent "simple" method presented in this paper. [It should be pointed out that in arriving at her figures the author included all cases living at 5 yrs. with or without disease; therefore, the 5-yr.-cure rate would be significantly less.]—*S. L. Perzik, M.D.*

Wille, Camillo [Norwegian Rad. Hosp., Oslo, Norway]: **Malign tumours in the nose and its accessory sinuses.** Acta oto-laryng. [suppl. 65]: 1-58, 1947.—The author reviews 220 cases of cancer of the nose and accessory nasal sinuses treated at the Norwegian Radium Hospital from 1932 to 1944. The group comprised 1.62% of all cancer cases. Regional node metastases were present in 35.5%, distant, in 9.1% of the series. 73.6% had carcinoma, 6.8% sarcoma, 2.3% mixed tumors, and 17.3% either unclassified (4.1%) or not biopsied. Metastases were reported as late as 21 yrs. after the appearance and control of the primary lesion. The best 5-yr. salvage (18.1%) occurred in 33 patients treated by radical surgery followed by intensive irradiation; the poorest (6.3%), in 95 cases treated by irradiation alone. The specific nature of the surgery or the detailed radiation factors used are not given. There are numerous analytical tables which are redetailed in the body of the report. [It is not possible to determine the basic figures used by the author in arriving at his end-result statistics.]—*S. L. Perzik, M.D.*

LARYNX

Baker, Herbert Koepp [Univ. Illinois Coll. Med., Chicago]: **The rehabilitation of the laryngectomized.** Tr. Am. Acad. Ophth. [1947]: 227-233, Jan./Feb., 1948.

Barry, William [Univ. Kansas Sch. Med., Kansas City]: **Cancer of the larynx—10-year review of 74 cases.** J. Kansas M. Soc. 49: 195-196, May, 1948.

Broughton-Barnes, E.; Duthie, E. S., & Jolles, B. [Gen. Hosp., Northampton, Eng.]: **Case of sarcoma of the larynx.** Brit. M. J. 1: 1237, June 26, 1948.

Kemler, Joseph I. [Baltimore, Md.]: **Bilateral thyrotomy for carcinoma of the larynx.** Tr. Am. Acad. Ophth. [1948]: 510-512, May/June, 1948.

Lavrand, A., & Desorgher, G.: Quatre cas de laryngectomie totale par le procédé de squelettisation du larynx. [**Four cases of total laryngectomy by the method of skeletization of the larynx.**] J. d. sc. méd. de Lille 66: 56-64, Feb. 1, 1948.—Epitheliomas.

Sayago, Carlos, & Segers, Alfredo Mario: Tratamiento del cáncer de laringe. [**Treatment of laryngeal carcinoma.**] Prensa méd. argent. 35: 414-416, Mar. 5, 1948.

BRONCHI

Bariéty, Maurice; Delarue, Jacques, & Paillas, Jean [Paris, France]: **Les formes histologiques des cancers bronchiques.** [**Histological forms of bronchial cancer.**] Presse méd. 56: 238-239, Mar. 31, 1948.

Brunner, A. [Chir. Univ.-Klin. Zürich, Swtz.]: **Diagnose und Therapie des bronchialkarzinoms.** [**Diagnosis and treatment of bronchial carcinoma.**] Helvet. chir. acta 14: 386-388, Oct., 1947.

Geyer, A., & Kerjan, L. [Hôp. maritime de Lorient, France]: **Un nouveau cas de cancer broncho-pulmonaire primitif. Diagnostic par inclusion des crachats à le paraffine.** [**Another case of primary bronchopulmonary cancer. Diagnosis by embedding sputum in paraffin.**] Rev. méd. nav. 2 (4): 355-357, 1947.

Howes, William E. [New York City]: **Bronchial adenoma.** Dis. of Chest 14: 427-436, May/June, 1948.—Review of the literature and 2 case reports.

Knppert, A. [Med. Univ.-Poliklin. Bern, Swtz.]: **Dns Krankheitsbild und die Differentialdiagnose des Bronchinlndenoms. [Disease picture and differential diagnosis of bronchial adenomn.]** Schweiz. med. Wchnschr. 78: 26-31, Jan. 17, 1948.—Review and 4 case reports.

Kraus, Alvin R.; Melnick, Perry J., & Weinberg, Joseph A. [Birmingham Veterans' Adm. Hosp., Van Nuys, Calif.]: **Myoblnstomn of the bronchus.** J. Thoracic Surg. 17: 382-389, June, 1948.—Case report.

Llambés, Juan, & Moreno, Rufino [Havana, Cuba]: **La forma esofágica del cáncer broncopulmonar. [Esophageal picture of bronchopulmonary cancer.]** Prensa méd. argent. 35: 130-134, Jan. 16, 1948.

Marest, Alphonse: **Deux cas de cancer bronchopulmonaire à forme cavitaire. [Two cases of the cavitary form of bronchopulmonary cancer.]** Hôpital 36: 40-41, Feb., 1948.

Penta, Arthur Q. [Ellis Hosp., Schenectady, N. Y.]: **The role of bronchoscopy in clinical medicine and surgery.** Dis. of Chest 14: 366-385, May/June, 1948.

Reitz, Hnrvey E. [M. C., U. S. Navy]: **A review of present methods in the early diagnosis of bronchogenic carcinoma.** U. S. Nav. M. Bull. 48: 198-206, Mar./Apr., 1948.—With 5 case reports.

LUNG

Bourret, J., & Fraisse, H.: **Cancer pulmonaire et traumatisme. [Cancer of the lung and trauma.]** J. de méd. de Lyon 29: 123-130, Feb. 20, 1948.—Review and report of 2 cases. The author suggests any relationship should be accepted only with the greatest reservation.—*M. C. J.*

Bradshaw, Howard H. [Bowman Gray Sch. Med., Wake Forest Coll., Winston-Salem, N. C.]: **Primary cancer of the lung.** North Carolina M. J. 9: 186-189, Apr., 1948.—General discussion.

Churchill, Edward D. [Massachusetts Gen. Hosp., Boston]: **Primary carcinoma of the lung.** J. A. M. A. 137: 455-461, May 29, 1948.—This is a comprehensive discussion of pulmonary cancer which covers in detail: the problem of early detection; the responsibility of the general practitioner, roentgenologist, and expert consultant for early diagnosis; methods of diagnosis and points of differential diagnosis; surgical treatment; criteria of operability; survival expectancy; nonsurgical treatment.—*D. A. S.*

Clemmesen, J., & Busk, T. [Nat. Anti-Cancer League, Copenhagen, Den.]: **On the apparent increase in the incidence of lung cancer in Denmark, 1931-1945.** Brit. J. Cancer 1: 253-259, Sept., 1947.—Official Danish mortality figures show an apparent rise in lung cancer among males: since 1931 an increase from about 5 per 100,000 in the capital to about 25 per 100,000 living in 1945, while the corresponding figures for females amount to 4 and 7 per 100,000 respectively. Thus the sex ratio has changed from about 5:4 to about 3:1. An analysis of the material from the Central Tuberculosis Station of Copenhagen from 1936 to 1945 shows a slight increase in the frequency of lung cancer but less pronounced and less constant, and the sex ratio for cases more than 45 yrs. of age has been 8 men to 1 woman. If the results from Copenhagen can be generalized, it seems that the apparent increase in lung-cancer mortality is, to a very large extent, conditioned by improvements in diagnosis and it can be expected to continue until the sex ratio amounts to about 8 males to 1 female.—*Auth. Summ.*

Fischer, J. W. [Cook Co. Hosp., Chicago, Ill.]: **Neoplastic involvement of pericardium producing the syndrome of constrictive pericarditis.** Am. Heart J. 35: 813-819, May, 1948.—Case report: massive pericardial metastases from primary carcinoma of lung.

Israel, René: **Diagnostic précoce du cancer pulmonaire primitif. [Early diagnosis of primary cancer of the lung.]** Rev. gén. de clin. et de thérap. 61: 565-568, Dec. 18, 1947.

Kennaway, E. L., & Kennaway, N. M. [St. Bartholomew's Hosp., London, Eng.]: **A further study of the incidence of cancer of the lung and larynx.** Brit. J. Cancer 1: 260-298, Sept., 1947.—The death certificates for cancer of the lung and of the larynx in males from England and Wales for the years 1921–38 inclusive, numbering 38,418, have been investigated and the periods 1921–32 and 1933–38 are compared. The 63 occupations examined employ about 30% of the male population aged 20 and upwards. Sources of error in statistical work on death certificates are discussed. The increase in the recorded cases of lung cancer cannot be attributed to any increase of data obtained by autopsy. The agricultural and coal-mining industries show a low incidence of cancer of the lung and of the larynx. A group of open-air occupations, where there is exposure to the dust of roads, has ratios above 100 for cancer of the lung and of the larynx, with the exception that motor drivers have a normal liability to cancer of the larynx. But the comparative incidence of cancer of the lung is not increasing distinctly in any of these occupations, and in the paviours, street masons, concretors, and asphalters there has been a distinct fall in the ratio. The occupations in which there is a liability to silicosis do not show a high incidence of cancer of the lung, but there are in the literature some studies of small numbers of cases in which the two conditions were associated. Cases of cancer of the lung have occurred in some occupations involving exposure to asbestos. In the death certificates examined, and in the Reports of the Chief Inspector of Factories, no occupations involving exposure to any kind of dust, except those concerned with asbestos, arsenic, and nickel, which

employ very small numbers, have been found in which there might be an increased incidence of cancer of the lung. Workers exposed to coal-gas and tar tend to show an increased prevalence of cancer of the lung, but in the later period studied the incidence does not exceed 2½ times that of the general population. Occupations concerned with the supply of alcohol have a high incidence of cancer of the larynx. The later period studied shows a considerable decrease in the occurrence of cancer of the lung in those engaged in the preparation and sale of tobacco. The very moderate ratio (125) for cancer of the lung in medical men is important in regard to the view that the recent rapid increase in recorded deaths from cancer of the lung is due to the detection of more cases by improved diagnosis, for this is an occupation where the availability of the existing methods for the detection of cancer is presumably at a maximum. No special occupations have been found, among the 63 examined, to which the increase in the total of cases of cancer of the lung can be attributed. This increase is now so great that the incidence upon any such occupations would have to be very high indeed. No evidence has been found that tarring of roads has affected the incidence of cancer of the lung. Such data as are available suggest that coal tar in the atmosphere, whether derived from roads, domestic chimneys, or any other source, does not cause an exceptionally high incidence of cancer of the lung. Cotton mule spinners show an especially small liability to cancer of the lung, although they inhale air sprayed with an oil which produces cancer of the skin. Much further work is required on the factors which regulate the penetration of particles and droplets of various shapes and sizes into the air passages. The higher mortality from cancer of the lung in towns (Stocks), the low mortality in agricultural occupations, and the absence of social gradient (Stevenson) are compatible with an etiological factor in the air such as coal smoke. But in any comparison of urban and rural areas, the question of facilities for diagnosis must be considered. Soot is probably a decreasing contaminant of the air owing to the substitution of other sources of heat for the domestic fire, which is the chief source of soot-containing smoke. Hence coal smoke does not account well for any recent increase in cancer of the lung. Among various possible factors which have been suggested to account for the increase is tobacco smoke; the consumption of tobacco has risen, and so has the percentage of it smoked in the form of cigarettes, of which the smoke is often inhaled; such an effect of tobacco would accord well with the absence of social gradient.—*Auth. Summ.*

Ochsner, Alton; DeBakey, Michael, & Dixon, Leonard [Tulane Univ. Louisiana Sch. Med., New Orleans]: **Carcinoma of the lung.** Postgrad. Med. 3: 427-440, June, 1948.

Orsi, Aldo: Fístulas torácicas espontáneas por cáncer de pulmón y por tuberculosis pulmonar. [Spontaneous thoracic fistulas in cancer of the lung and pulmonary tuberculosis.] Rev. Asoc. méd. argent. 61: 724-727, Oct. 15-30, 1947.

Roncallo, E., & Peluffo, G. [Univ. Genoa, Italy]: **Su di un caso di associazione di carcinoma polmonare primitivo con metastasi ghiandolari e granuloma maligno addominale. [A case of primary carcinoma of the lung associated with lymph-node metastases and abdominal lymphogranulomatosis.]** Pathologica 39: 231-238, Sept./Oct., 1947.

Taiana, Jorge A.; Boragina, Rodolfo C., & Schieppati, Eduardo: Lobotomía prefrontal bilateral en el cáncer de pulmón. Tres casos. [Bilateral prefrontal lobotomy in cancer of the lung. Three cases.] Prensa méd. argent. 35: 449-452, Mar. 12, 1948.—Lobotomy done in inoperable cancer for mitigation of pain.

Wodehouse, G. E. [Univ. Toronto, Ont.]: **Hemangioma of the lung. A review of four cases, including two not previously reported, one of which was complicated by brain abscess due to *H. influenzae*.** J. Thoracic Surg. 17: 408-415, June, 1948.

Woodman, DeGraaf [Columbia Univ., Coll. Phys. & Surgeons, New York City]: **The diagnosis of primary carcinoma of the lung.** New York State J. Med. 48: 1359-1363, June 15, 1948.

TUMORS OF INFANCY AND CHILDHOOD

Berezin, S. W. [Lincoln Hosp., New York City]: **Sharnoff, J. G., & Stein, J. D.: Primary hemangioendothelioma of the liver in infancy. Report of a case.** New England J. Med. 238: 906-907, June 24, 1948.—Autopsy findings in a 9-day-old white female infant.

Bonse, G. [Städt. Krankenanst. Bremen, Germany]: **Zur Strahlentherapie maligner Tumoren in Kindesalter. [Irradiation of malignant tumors in childhood.]** Strahlentherapie 77 (1): 39-46, 1947.—The author reports on the malignant tumors of childhood seen during the past 10 yrs.

Campbell, Meredith F. [New York Univ. Coll. Med., New York City]: **Bilateral embryonal adenomyosarcoma of the kidney (Wilms tumor).** J. Urol. 59: 567-571, Apr., 1948.—Two case reports: 18-month- and 24-day-old infants.

Haley, Harold B. & Jackson, Arnold S. [Jackson Clin., Madison, Wis.]: **Hemangioendothelioma of the salivary gland.** Am. J. Surg. 75: 725-728, May, 1948.—Case report: 6-wk.-old male infant.

Hicken, N. Frederick; Stevenson, Vernon L.; Carlquist, John H., & Coray, Q. B. [Univ. Utah M. Sch., Salt Lake City]: **Multiple duplicative cysts of the duodenum causing acute intestinal obstruction in a girl five and one-half years of age.** Am. J. Surg. 76: 92-98, July, 1948.

Kretschmer, Herman L. [Presbyterian Hosp., Chicago, Ill.]: **Embryoma of the testicle in a**

five-year old child. Am. J. Surg. 76: 99-101, July, 1948.

Leibner, I. Wallace [Jewish Hosp. Brooklyn, New York City]: Brain tumors in infancy. A report of seven cases. Pediatrics 1: 346-363, Mar., 1948.—Seven cases of brain tumors occurring in infants (6 males, 1 female) are presented. 3 arose in the cerebellum; the other 4 were supratentorial. The tumors included 2 medulloblastomas, 1 spongioblastoma polare, 1 ependymoma, 1 astrocytoma, and 1 hemangioblastoma. The 7th case probably was also medulloblastoma. 1 of the proved medulloblastomas was supratentorial, which is unusual as far as location is concerned. The hemangioblastoma arose in the cerebrum. The location of this tumor is also a rare one and to my knowledge, it is the first case of its type reported in an infant in whom full recovery occurred following removal of the tumor. The diagnosis was unsuspected in 4 cases. 3 of these infants were believed to be suffering from congenital hydrocephalus while the 4th was thought to be afflicted with encephalitis. The ways in which the correct diagnosis might have been made are discussed. Since bizarre clinical patterns are sometimes produced by brain tumors in infants and the diagnosis frequently overlooked, the possibility should be kept in mind by the pediatrician in considering the differential diagnosis of conditions producing signs referable to the nervous system.—*Auth. Summ.*

Wass, S. H.: Melanotic adamantinoma of the mandible in a child aged 5 months. Proc. Roy. Soc. Med. 41: 281-283, May, 1948.

RESEARCH (GENERAL)

Anon.: Imperial Cancer Research Fund. Annual report. Brit. M. J. 1: 995, May 22, 1948.

Barnard, Robert D. [Terrace Heights Hosp., Hollis, L. I., N. Y.]: Similarity to heparin of the clotting inhibitor in acute leucemia and the significance of hyperheparinemia in estrapenic cholinergic states. Science 107: 571-572, May 28, 1948.

Bass, Allan D., & Freeman, Marion L. H. [Syracuse Univ. Coll. Med., N. Y.]: Effect of folic acid and bis (β-chloroethyl) sulfide (mustard gas) on transplanted mouse lymphosarcoma. Proc. Soc. Exper. Biol. & Med. 66: 523-525, Dec., 1947.—"Synthetic folic acid," "Folvite," or "Teropterin" in the dosage employed do not produce regression in transplanted $6C_3HED$ tumors in C_3H mice. Administration of synthetic folic acid partially inhibits the effect of bis (β-chloroethyl) sulfide on lymphosarcoma $6C_3HED$. —*Auth. Summ.*

[Cleveland, Rucker] [Inst. Divi Thomae, Cincinnati, Ohio]: Current methods of preparation of extracts of animal tissues for use in bacteriologic and cancer investigations. Stud. Inst. Div. Thom. 5: 55-64, 1946-47.

Ellinger, Friedrich [Long Island Coll. Med., New York City]: Influence of pharmacological agents on effects of irradiation. Radiology 50: 234-243, Feb., 1948—A standardized technique is given to measure qualitatively the effects of x-rays on mice. The criteria are: the survival time and lethality of several dose levels of x-rays and the effects of these doses, graded from 0 effect to 4+, on the histology of the spleen and the fat content of the liver. It is suggested that these criteria may be used in an assessment of the influence of various pharmacological agents on radiation injury in mice, and the author tested several compounds. Desoxycorticosterone acetate produced a decrease in mortality in mice irradiated with the LD_{50} dose of x-rays; the livers showed less accumulation of fat, but the degree of splenic injury was unchanged. Pregnanolene did not alter the LD_{50} effect nor change the degree of fat accumulation in the liver. The vitamin-B complex caused a decrease in the accumulation of fat in the liver of the irradiated mice; vitamin C had a similar, but less definite, effect. The spleens were not protected in the vitamin-treated irradiated animals. —*D. A. Karnofsky, M.D.*

Goldhaber, Paul; Cornman, Ivor, & Ormsbee, Richard A. [Sloan-Kettering Inst., New York City]: Experimental alteration of the ability of tumor cells to lyse plasma clots *in vitro*. Proc. Soc. Exper. Biol. & Med. 66: 590-595, Dec., 1947.—Mouse Sarcoma 180 cells, in the presence of mammalian serum, cause lysis of chicken plasma clots. Mammalian aqueous humor has slight influence on the fibrinolytic process. When Sarcoma 180 is grown in the presence of avian serum, no lysis occurs. If a sufficient quantity of chicken serum is added to a supernatant fluid containing mammalian serum, there is a decrease in the amount of clot lysis. Lysis of the plasma clot by Sarcoma 180 does not occur when mammalian serum previously heated to 56° C. for 3 hrs. is used, or when all serum is omitted from the supernatant. The different degrees of lysis obtained when sera from various mammalian orders are used may be due to differences in the amount of profibrinolysin contained in the various sera. There are two factors necessary for the lytic mechanism, tentatively classified as a profibrinolysin from the serum, and an activator of the profibrinolysin derived from the tissue.—*Auth. Summ.*

Grattarola, Renzo [Univ. Milano, Italy]: I vari aspetti della cellula-cancro e gli alterni rapporti fra acido ribonucleinico e timonucleinico. [The varying appearance of the cancer cell and the different response to ribonucleic and to thymonucleic acids.] Tumori 21 (6): 329-337, 1947.

Jacobson, L. O.; Marks, E. K.; Gaston, E. O.; Simmons, E. L., & Block, M. H. [Argonne Nat. Lab., Chicago, Ill.]: Studies on radiosensitivity of cells. Science 107: 248-250, Mar. 5, 1948.—Hyperplasia of the erythrocyte precursors in the bone marrow of rabbits was induced by phlebotomy or by the hemolytic action of acetyl phenylhydrazine. The effect of a single, whole-body, 800-r dose of x-rays on these ani-

mals and on animals with normal marrows was compared. The animals in which regenerative anemia had been produced prior to irradiation with 800 r developed no further anemia. Irradiated normal animals developed a moderate anemia. The recovery time in both groups was comparable (23 days). The mean reticulocyte value of the phenylhydrazine-injected, x-rayed animals was reduced below the normal control value on the 6th post-irradiation day only. The phlebotomized group responded to irradiation in a manner comparable to those treated with phenylhydrazine and x-rays. In the normal animals the erythropoietic tissue in the bone marrow and the spleen was essentially completely destroyed within 3 days after 800 *r;* and a relatively slow recovery ensued beginning on the 7th to 9th day. In the group previously treated with phlebotomy or phenylhydrazine, the erythropoietic tissue in the bone marrow and spleen was only partially destroyed after 800 r. Sufficient viable erythropoietic tissue remained to permit an essentially normal production of erythrocytes. The authors feel these data would tend to indicate that erythroblast vulnerability to irradiation injury was not enhanced by increased mitotic activity and proliferation; and that this hyperplastic tissue sustained less histological injury than the normal.—*J. H. Burchenal, M.D.*

Kidder, George W. [Amherst Coll., Amherst, Mass.]: **The nutrition of monocellular animal organisms.** Ann. New York Acad. Sc. 49 (1): 99-110, 1947.

Lasnitzki, Ilse [Strangeways Res. Lab., Cambridge, Eng.]: **The effect of beta rays on cells cultivated *in vitro*.** Brit. J. Radiol. 21: 265-269, June, 1948.

Ormsbee, Richard A.; Cornman, Ivor & Berger, Ruth E. [Sloan-Kettering Inst., New York City]: **Effect of podophyllin on tumor cells in tissue culture.** Proc. Soc. Exper. Biol. & Med. 66: 586-590, Dec., 1947.—Podophyllin exerts a selective damaging effect on mouse-tumor cells in tissue culture over the concentration range 0.08-20.0 mg/l. This damaging effect is more easily reversible in normal than in tumor cells. Podophyllotoxin is not as effective as podophyllin in causing selective tumor damage. In vivo studies with tumor-bearing mice confirm the selective tumor-damaging effects of podophyllin which were first noted in tissue-culture preparations.—*Auth. Concl.*

Riley, Vernon T. [Nat. Cancer Inst., Bethesda, Md.]: **Application of chromatography to segregation studies of the agent of chicken tumor I (Rous sarcoma virus).** Science 107: 573-575, May 28, 1948.—Preliminary report.

Robbins, William J. [Columbia Univ., New York City]: **Some basic contributions to the cancer problem from the study of plants.** Ann. New York Acad. Sc. 49 (1): 75-86, 1947.

Stolinsky, Aaron [San Francisco, Calif.]: **Some newer developments in cancer research. A review of the literature.** M. Rec. 161: 282-286, May, 1948.

ANIMAL EXPERIMENTATION

Bittner, John J. [Univ. Minnesota M. Sch., Minneapolis]: **The mammary tumor milk agent.** Ann. New York Acad. Sc. 49 (1): 69-73, 1947.

Browning, Henry C. [Nat. Cancer Inst., Bethesda, Md.]: **Heterologous and homologous growth of transplants during the course of development of spontaneous mammary tumors in C3H mice.** J. Nat. Cancer Inst. 8: 173-189, Feb., 1948.—The property of autonomy, as shown by the ability to grow in alien strains and species, was studied in spontaneous mammary tumors of C3H mice by growing them in the anterior chamber of the eyes of C57 black and dba mice, guinea pigs, and rabbits. In solitary tumors, autonomy was not present in the very young neoplasm. It appeared gradually with tumor development and reached a peak in old solitary tumors where metastasis might be expected. Metastases themselves always showed autonomy. The simple course of autonomy development in solitary mammary tumors was upset by the appearance of other tumors in the same animal. 2 such tumors might exhibit degrees of autonomy in correspondence to their ages, show an equal degree of autonomy despite great differences of tumor age, or have autonomy in inverse relation to age of the tumor. Autonomy might be increased or be unchanged after partial excision of a tumor. Growth rate in homologous transfer of solitary tumors corresponded to the degree of autonomy present. This relation was upset in multiple tumors. No correlation was found between histological structure and autonomy or growth rate in homologous transfer. Grossly detected lesions of less than 0.2 cm. in diameter were either squamous-cell metaplasia or adenomas. The former group often regressed and never progressed; nor did they show autonomy or homologous growth. Autonomy was best shown in young recipient animals. Neither sex nor size of the transplant had an obvious effect. Autonomy was more uniformly exhibited in animals of pure strain. Heterologous growth of C3H tumors was of much shorter duration but of the same character as that found by Greene and his co-workers for various human, rabbit, and avian cancers. Complete regression was always the ultimate fate of heterotransplants.—*Auth. Summ.*

Cowen, P. N. [Edinburgh Univ., Scotland]: **Some studies on the action of urethane on mice.** Brit. J. Cancer 1: 401-405, Dec., 1947.—The number and size of lung adenomas produced in RIII, CBA, and C57 mice by urethane decreased in that order. This is the same order as the incidence of spontaneous lung cancer. Compared with a group given similar treatment with veronal (which was noncarcinogenic), the urethane-treated animals showed a high incidence of infectious diseases. No pleuropneumonia-like organisms were present in the lungs of the urethane-treated mice. Treatment with urethane

did not cause male sterility. No action on embryonic growth was noted.—*Auth. Summ.*

Dury, A., & Robin, E. D. [George Washington Univ. Sch. Med., Washington, D. C.]: Urethane-induced lymphopenia in normal and adrenalectomized rats. Endocrinology 42: 320-325, Apr., 1948.—A leukopenia and an absolute lymphopenia of similar magnitude were induced in normal intact and normal adrenalectomized rats following the intraperitoneal administration of a 10% urethane solution. The evidence presented here showed that the adrenal glands were not involved in these changes in the blood picture. A possible mode of urethane action was discussed. A relation of urethane with the adrenal mechanism was suggested by a polymorpholeukocytosis which was induced in urethanized rats 20 hrs. after adrenal cortical stimulation.—*Auth. Summ.*

Ferro, A. [Univ. Padova, Italy]: Formazione di tumori in seguito a trapianti autologhi di ghiandola mammaria nel topo bianco. [Tumor formation after autologous transplantation of the mammary gland in the white rat.] Tumori 21 (4/5): 217-228, 1947.—In 5.4% instances adenocarcinoma followed the transplantation.

Foulds, L. [Imperial Cancer Res. Fund, London, Eng.]: Mammary tumours in hybrid mice: a sex-factor in transplanation. Brit. J. Cancer 1: 362-370, Dec. 1947.

Greene, Harry S. N., & Newton, B. L. [Yale Univ. Sch. Med., New Haven, Conn.]: Evolution of cancer of the uterine fundus in the rabbit. Cancer 1: 82-99, May, 1948.

Imagawa, David T.: Green, Robert G., & Halvorson, H. Orin [Univ. Minnesota M. Sch., Minncapolis]: A precipitin test for antigens present in mouse tissues containing the milk agent. Proc. Soc. Exper. Biol. & Med. 68: 162-166, May, 1948.

Kahler, Herbert, & Buchanan, George [Nat. Cancer Inst., Bethesda, Md.]: Effect of the injection of various substances upon the in vivo electrical resistance of rats. J. Nat. Cancer Inst. 8:163-168, Feb., 1948.—The resistance of animal tissue in vivo was measured at 5000 cycles. Intraperitoneal injection of massive doses of sugar was followed by an increase of body and tumor-tissue resistance. Other nonelectrolytes behaved similarly. Injection of NaCl had the opposite effect. Determinations were made upon the volume, electrical conductivity, glucose, and chloride concentration of the peritoneal fluid at successive time intervals following glucose administration. These effects were related to shifts in body electrolytes and water. Intravenous injection of sugar was followed by an increase in resistance. From these experiments, it is concluded that the interstitial fluid conductivity is the chief component of the tissue contributing to these effects, excluding unknown membrane changes.—*Auth. Summ.*

Kaplan, Henry S. [Nat. Cancer Inst., Bethesda, Md.]: Comparative susceptibility of the lymphoid tissues of strain C57 black mice to the induction of lymphoid tumors by irradiation. J. Nat. Cancer Inst. 8: 191-197, Feb., 1948.—Young mice of strain C57 black were killed at successive intervals after fractional whole-body irradiation, and the lymph nodes, spleens, and thymus glands subjected to gross and histological examinations and to bioassay. 15 of 28 mice (54%) developed lymphoid tumors within 57 to 135 days after the beginning of irradiation. Most of the tumors were confined to the thymus gland, in 4 instances to just 1 lobe, and in no case had the disease spread outside the thorax. The only positive bioassay arose from 3 thymic-tissue fragments, 1 of which came from a mouse that revealed no histological evidence of a lymphoma. It is evident that lymphoid tumors in irradiated young mice of this strain regularly make their first appearance in the thymus gland and secondarily spread to the mediastinum and lungs before invading distant lymphoid structures. It is, therefore, concluded that such lymphoid tumors are initially monocentric in origin, differing biologically from other neoplastic processes chiefly in their greater ability to disseminate and to invade the blood stream. Some of the factors which appear to modify the relative susceptibility of the lymphoid tissues to leukemogenic agents are discussed.—*Auth. Summ.*

Klüver, Heinrich [Univ. Chicago, Ill.], & Weil, Arthur: Carcinomas of the tongue in monkeys and pathologic changes in the central nervous system. J. Neuropath. & Exper. Neurol. 7: 144-153, Apr., 1948.—The histopathology of the central nervous system of 2 cases of carcinoma of the tongue in rhesus monkeys is described. While the carcinoma in the 1st monkey was spontaneous in origin, that in the 2nd was produced by an injection of an emulsion of the carcinomatous tissue from the 1st monkey into the tongue of the 2nd. Motor nuclei of the brain stem and the anterior horns of all spinal-cord segments were affected. The lesions were characterized by intracytoplasmic vacuoles, frequently containing a small, roundish body, and by other severe cell changes. In order to explain the limited distribution of the lesions in the brain stem and spinal cord, Galkin's experiments have been cited. They demonstrate direct connections between the lymphatic system of the pharynx and the subarachnoid spaces. It is assumed that the etiological factor responsible for the damage of the neurons (carcinoma toxin? virus?) invaded the central nervous system via such lymphatics.—*Auth. Summ.*

Lewis, Margaret Reed [Wistar Inst., Philadelphia, Pa.], & Goland, Philip P.: In vivo staining and retardation of tumors in mice by acridine compounds. Am. J. M. Sc. 215: 282-289, Mar., 1948.

Luther, W., & Lorenz, W. [Marburg, Germany]: Uber die histologischen Veränderungen der Mäusemilz nach Röntgenbestrahlung und Urethanbehandlung. [The histological changes in the spleen of the mouse after x-ray irra-

diation and urethane treatment.] Strahlentherapie 77 (1): 27-32, 1947.

Maculla, Esther Sylvia [Yale Univ. Sch. Med., New Haven, Conn.]: **The immunochemistry of mouse tissue components: I. Comparative antigenic composition of normal mouse tissues. II. The comparative antigenic composition of homologous and heterologous mouse tumor transplants. III. A comparison of the antigenic composition of embryonic mouse organs with that of adult mouse organs and with mouse tumors.** Yale J. Biol. & Med. 20: 299-314, Jan.; 343-368, Mar.; 465-472, May, *1948.—II.* Characteristic reaction patterns have been obtained for antisera evoked by antigenic components of mouse tumors. These patterns reflect the immunological relationships between tumor tissues and normal tissues. The following generalizations were drawn: (a) All tumors appear to possess intracellular antigenic components in common with adult mouse spleen and lung. (b) Some tumors appear to possess a component or components that may be distinct from those of normal tissues. (c) The nucleoproteins derived from mouse tumors are immunologically distinct from the nucleoproteins obtained from normal mouse organs. (d) Some tumors, of common cytological origin (e.g., MT-25 and MT-26, N. F. and L. F.), appear to possess closely related components. Other tumors, for which no common cytological origin can be claimed, or that have no apparent morphological similarity (e.g., MT-8 and lymphosarcoma), also exhibit close antigenic relationships.

When mouse tumors are grown in the anterior chamber of the guinea-pig eye, their antigenic composition is altered. Components obtained from transplants of mouse tumors grown in the guinea pig either no longer react with antisera evoked by components of mouse tumors or react in considerably reduced titer. Antisera developed to some mouse tumor components, especially to the residues and nucleoproteins of tumors, react more widely with components of guinea-pig tissues than do antisera induced by components of normal mouse organs. No correlation between the ability of tumors to grow heterologously and any specific antigenic component could be demonstrated. The significance of these observations has been discussed.

III. The antigenic relationships among the intracellular components of adult and embryonic tissues have been examined. (a) It has been found that the antigenic components of certain adult organs, like liver and lung, appear similar to their embryonic counterparts. (b) It has also been observed that the antigenic components of other adult organs, like spleen and kidney, are immunologically distinct from those of the corresponding embryonic organs.

Antigenic relationships among tumor tissues and embryonic tissues have been described. (a) 2 tumors reacted very widely with embryonic tissues; 4 reacted very selectively. (b) 6 tumors appeared to possess components present in embryonic liver, despite the fact that they did not all appear to possess components present in adult liver. (c) The absence of reactivity between tumor antisera and embryonic spleen was noted, whereas reactivity of these antisera with adult spleen was always observed. The possible significance of these observations was discussed.—*Auth. Concl.*

Orr, J. W. [Univ. Leeds, Eng.]: **The histology and histogenesis of pulmonary adenomata of mice.** Brit. J. Cancer 1: 316-322, Sept., 1947.—The histology and histogenesis of the pulmonary adenomata of mice are described, based on the examination of 433 animals, of which 191 showed fully formed tumors. The material was derived from several experiments, involving various treatments, and 5 pure inbred strains as well as stock mice. The adenomata are believed to develop in foci of chronic collapse inflammation, and to be derived from the bronchiolar epithelium. The majority of them are regarded as benign, but there was one definitely malignant tumor.—*Auth. Summ.*

Orr, J. W. [Univ. Leeds, Eng.]: **The induction of pulmonary adenomata in mice by urethane.** Brit. J. Cancer 1: 311-316, Sept., 1947. —The findings of Nettleship and Henshaw (1943) that treatment with urethane gives rise to a greatly increased incidence of pulmonary adenomata in mice have been confirmed. The effect has been found in all mice tested, though some strains are more susceptible than others. Various other anesthetic substances gave negative results. The immediate effect of urethane is to set up chronic inflammation in the lungs, and the adenomata appear to arise as the result of further changes in the inflammatory lesions; in some cases there is evidence that they are derived from proliferation of the bronchial epithelium. Not all the macroscopic nodules are tumors; some regress if treatment is discontinued. The present series contained one malignant tumor, the histology of which was different from that of the adenomata.—*Auth. Summ.*

Orr, J. W., & Bielschowsky, F. [Univ. Leeds, & Univ. Sheffield, Eng.]: **The histology of pulmonary tumours of the rat induced by 2-acetylaminofluorene.** Brit. J. Cancer 1: 396-400, Dec., 1947.

Rose, S. Meryl, & Wallingford, Hope M. [Smith Coll., Northampton, Mass.]: **Transformation of renal tumors of frogs to normal tissues in regenerating limbs of salamanders.** Science 107: 457, May 7, 1948—Normal tissues in regenerating limbs dedifferentiate and revert to an embryonic state, after which the cells grow and differeniate into new tissues. Because cancerous tissue seems to be abnormally differentiated, an attempt has been made to obtain its dedifferentiation and subsequent transformation to normal tissue. In order that former cancer cells might be recognized if they did revert to normal, frog tumors with small nuclei were transplanted to limbs of salamanders which have cells with much larger nuclei.

Small pieces of rapidly growing renal tumors from *Rana pipiens* were transplanted subcutane-

ously to forelimbs of *Triturus viridescens*. After the small pieces of frog tumor were established and had started to grow and invade the tissues of the salamanders' limbs, the limbs were amputated through the cancer. In all cases regeneration was normal. The regenerates, with a section of the old limb, were fixed and studied histologically. During the early stages of regeneration, when the salamander tissues were just beginning to differentiate, patches of unorganized frog cells were observed. In slightly later stages patches of frog muscle, cartilage, and fibrous connective tissue can be seen interspersed and blending with the corresponding salamander tissues. The frog tissues, in addition to having smaller nuclei, were found to stain somewhat differently and are invaded by leucocytes of the host. Most of the patches of normally differentiated frog tissue are adjacent to unchanged tumor remaining in the old part of the limb proximal to the level of dedifferentiation.—*Auth. Prelim. Rep't.* (Reprinted from SCIENCE.)

Santa Cruz, J. Z. [Univ. Santo Tomas, Coll. Med. & Surg., P. I.]: **Experimental liver cancer in rats produced by butter yellow.** J. Philippine M. A. 24: 1-9, Jan., 1948.

Selbie, F. R., & Robinson, R. H. M. [Middlesex Hosp., London, Eng.]: **Serial transmission of infectious papillomatosis in the domestic rabbit.** Brit. J. Cancer 1: 371-379, Dec., 1947.

Tannenbaum, Albert [Michael Reese Hosp., Chicago, Ill.]: **Effects of varying caloric intake upon tumor incidence and tumor growth.** Ann. New York Acad. Sc. 49 (1): 5-18, 1947.—There is considerable experimental evidence that caloric restriction inhibits the genesis or incidence of all types of mouse tumors that have been studied: induced skin tumors, induced sarcomas, spontaneous mammary carcinomas, spontaneous lung adenomas, spontaneous hepatomas, and spontaneous and induced leukemia. Fewer mice develop tumors, and these appear, on the average, at a later time. The inhibitory effect is dependent on the degree of caloric restriction, the type of tumor, and the dosage or potency of the carcinogen. It is probable that the main influence occurs during the development of the tumor rather than during the preparatory stage. The growth of tumors can be inhibited by caloric restriction, but the host also loses weight. Present evidence does not suggest that caloric restriction may affect the growth of tumors in a practical, useful way.—*Auth. Summ.*

White, Julius [Nat. Inst. Health, Bethesda, Md.]: **Experimental studies on leukemia in mice.** Proc. Inst. Med. Chicago 17: 130-136, June 15, 1948.

Winchester, William W., & Higgins, George M. [Mayo Clin., Rochester, Minn.]: **Pulmonary edema in leucemic mice following treatment with urethane.** Science 107: 568-569, May 28, 1948.

CHEMISTRY AND METABOLISM

Abul-Fadl, M. A. M., & King, E. J. [Postgrad. M. Sch. London, Eng.]: **The inhibition of acid phosphatases by formaldehyde and its clinical application for the determination of serum acid phosphatases.** J. Clin. Path. 1: 80-90, Feb., 1948.—The acid phosphatase in the serum and red cells, and that originating from the prostate gland are different. It is desirable to be able to inhibit one type without affecting the others. Incubation of serum with absolute alcohol will completely destroy the prostate enzyme fraction, but others may be inhibited. Formaldehyde will destroy the red-cell, but not the prostatic, acid phosphatase. A serum acid phosphatase after formaldehyde treatment (more than 5 King-Armstrong units) suggests prostatic carcinoma. Formaldehyde permits the use of hemolyzed serum, which ordinarily will give a high acid phosphatase. In doubtful cases, the use of formaldehyde inhibition and alcohol incubation procedure may be of confirmatory value.—*D. A. Karnofsky, M. D.*

Bach, S. J., & Lasnitzki, I. [Biochem. Lab., & Strangeways Res. Lab., Cambridge, Eng.]: **Some aspects of the role of arginine and arginase in mouse carcinoma 63.** Enzymologia 12: 198-205, Nov. 20, 1947.—The effect of arginine on the mitosis in mouse adenocarcinoma 63, grown in vitro [hanging-drop technique], was studied. The addition of various concentrations of arginine to the culture medium resulted in a considerable increase in mitosis. No effect of arginine was observed in similar cultures of normal embryonic mouse lung. Correlating the arginase content of various samples of the same tumor strain with their growth rate, it was found that slow-growing tissue contained twice as much enzyme as fast-growing tissue. An addition to the culture medium of ornithine, which is known to inhibit arginase, had a stimulating effect on the mitosis of the tumor, but not on that in normal lung tissue. The results suggest an inhibiting effect of arginase on the growth of the tumor investigated. The possibility of a new role for arginase in the defense mechanism of the organism against tumor growth is discussed.—*Auth. Summ.*

Barron, E. S. Guzman; Bartlett, Grant R., & Miller, Zelma Baker [Univ. Chicago, Ill.]: **The effect of nitrogen mustards on enzymes and tissue metabolism. I. The effect on enzymes.** J. Exper. Med. 87: 489-501, June, 1948.—Nitrogen mustards are powerful inhibitors for choline oxidase, acetylcholine esterase, and choline acetylase, half-inhibition of the first enzyme being produced with concentrations around 1×10^{-6} M; i.e., 10 times less than the LD_{50} values. Acetylcholine esterase and choline acetylase required higher concentrations. This inhibition seems to be due to the structural similarity of the ethylenimonium derivatives with choline and acetylcholine. A list of enzyme systems inhibited by nitrogen mustards is given.—*Auth. Summ.*

Barron, E. S. Guzman; Bartlett, Grant R.; Miller, Zelma Baker; Meyer, Joe, & Seegmiller, J. E. [Univ. Chicago, Ill.]: **The effect of nitrogen mustards on enzymes and tissue metabolism. II. The effect on tissue metabolism.** J. Exper. Med. 87: 503-519, June, 1948.—Nitrogen mustards at 40 times the MLD inhibited the respiration of all tissues studied but affected anaerobic glycolysis very little. The inhibiting effect increased with time. The respiration of lymphoid tissue was extremely sensitive to nitrogen mustard, for concentrations below the LD_{50} definitely inhibited the respiration of rabbit lymph nodes. In tissue slices, nitrogen mustards inhibited the oxidation of pyruvate and of *l*-amino acids and the utilization of NH_3. A number of synthesis reactions were also inhibited, such as the synthesis of carbohydrate, of creatine, and of urea. When added to growing seeds, nitrogen mustards inhibited their growth. In rats given lethal doses of nitrogen mustards, there were found complete inhibition of choline oxidation and strong inhibition of pyruvate oxidation by the kidney and partial inhibition of urea synthesis by the liver. Inhibition of bone-marrow respiration by nitrogen mustards was prevented by the addition of choline, and of dimethylaminoethanol plus methionine. The possible mechanism of nitrogen-mustard intoxication is discussed.—*Auth. Summ.*

Berenblum, I., & Shubik, P. [Univ. Oxford, Eng.]: **The role of croton oil applications, associated with a single painting of a carcinogen, in tumour induction of the mouse's skin.** Brit. J. Cancer 1: 379-382, Dec., 1947.—Mottram's finding that a single application of 3:4-benzpyrene, followed by repeated applications of croton oil, will induce tumors, is confirmed, and is shown to hold also for 9:10-dimethyl-1:2-benzanthracene. Mottram's other observation, that nonspecific hyperplasia, induced by croton oil *previous to* the single application of a carcinogen, leads to an increase in the number of tumors induced, is not confirmed.—*Auth. Summ.*

Berenblum, I., & Shubik, P. [Univ. Oxford, Eng.]: **A new, quantitative, approach to the study of the stages of chemical carcinogenesis in the mouse's skin.** Brit. J. Cancer 1: 383-391, Dec., 1947.—To study the stages of carcinogenesis by quantitative means, use was made of the technique, based on Mottram's work, whereby tumors of the mouse's skin may be induced by a single application of a carcinogen, followed by repeated applications of croton oil. When the croton-oil treatment was kept constant but different carcinogens were used for the initial painting, the tumor incidence varied from group to group but the average latent period remained the same. When the initial painting with the carcinogen was kept constant but the croton-oil treatment was delayed, the tumor incidence remained the same but the latent period varied, corresponding approximately to the lengths of the intervals free from treatment. It was concluded that the initial action in carcinogenesis constitutes a sudden and irreversible process, whereby a few normal cells are changed into permanently altered "latent tumor cells," which lie dormant among the non-neoplastic cells. The mechanism by which these latent tumor cells are made to develop into tumors is altogether different from that of the initial transformation. Some of the implications of these conclusions are discussed.—*Auth. Summ.*

Blout, Elkan R., & Fields, Melvin [Polaroid Corp., Cambridge, Mass.]: **On the infrared spectra of nucleic acids and certain of their components.** Science 107: 252, Mar. 5, 1948.—Preliminary results on the determination of infrared absorption in the region 700 to 1800 $cm.^{-1}$ of yeast ribonucleic acid, thymus desoxyribonucleic acid, and some of their chemical constitutents are given. Spectra were determined in the solid phase. One pure material could be differentiated from another by infrared spectra; e.g., ribonucleic acid from desoxyribonucleic acid by their absorptions at frequencies lower than 1100 $cm.^{-1}$; thymine (6 methyl uracil) from uracil and adenine by their absorptions between 900 and 1200 $cm.^{-1}$, and thymine and uracil differentiated in mixtures. This suggests differentiating between nucleic acids from different sources.—*J. H. Burchenal, M. D.*

Boyland, E. [Roy. Cancer Hosp. (Free), London, Eng.]: **Chemical carcinogenesis and experimental chemotherapy of cancer.** Yale J. Biol. & Med. 20: 321-341, Mar., 1948.

Calcutt, G., & Powell, A. K. [Mt. Vernon Hosp., London, Eng.]: **The control of some factors involved in experimental epidermal carcinogenesis.** Brit. J. Cancer 1: 323-327, Sept., 1947.—It is concluded that careful clipping of the fur is the best preparation of the skin [of a mouse] for detailed work. A stencil for use in standardizing the area to be treated is described. The question as to how much solvent to use in order to apply a given amount of carcinogen is discussed. It is shown that mice very rapidly lick off any reagent applied to the skin. The implications of this last finding in relation to work involving surface applications of reagents are discussed.—*Auth. Summ.*

Carminati, V., & Baglioni, T. [Inst. Naz. Studio e Cura dei Tumori, Milan, Italy]: **Di talune modificazioni indotte da alte dosi di estrogeni nel ratto maschio. Nota I. Osservazioni sul testicolo (didimo e epididimo), deferenti e vescicole seminali. [Some modifications induced by high doses of estrogens in the male rat. I. Observations on the testis (and epididymis), vas deferens, and seminal vesicles.]** Tumori 21 (6): 297-308, 1947.

Carruthers, Christopher, & Suntzeff, V. [Barnard Free Skin & Cancer Hosp., St. Louis, Mo.] **Cytochrome c in epidermal carcinogenesis in mice induced by methylcholanthrene.** Arch. Biochem. 17: 261-267, May, 1948.—The role of cytochrome c in epidermal carcinogenesis in mice was investigated. The enzyme was deter-

minced spectrophotometrically and polarographically and both procedures gave results of same order of magnitude. The cytochrome c content of normal, benzene-treated, and methylcholanthrene-treated epidermis is nearly the same, but there is a decrease of about 30% in the transplantable squamous-cell carcinoma. The relationship of cytochrome c to the activity of succinic dehydrogenase, apyrase, and cytochrome oxidase in epidermal carcinogenesis is briefly discussed. The polarographic method revealed that cytochrome c in the epidermis of mice is closely associated with, or bound to, another substance which cannot be separated from the cytochrome c by adsorption on aluminum oxide. In contrast to epidermis, the cytochrome c of mouse and rat liver, kidney, skeletal muscle, and heart can be removed by 1 or 2 adsorptions on aluminum oxide.—*Auth. Summ.*

Clark, Leland C., Jr. & Thompson, Haskell [Antioch Coll., Yellow Springs, Ohio]: **A new series of reagents for the colorimetric determination of steroids.** Science 107: 429-431, Apr. 23, 1948.

Dobriner, Konrad; Lieberman, Seymour, & Rhoads, C. P. [Sloan-Kettering Inst., New York City]: **Studies in steroid metabolism. I. Methods for the isolation and quantitative estimation of neutral steroids present in human urine.** J. Biol. Chem. 172: 241-261, Jan., 1948. —A description is given of the methods devised to determine the qualitative and quantitative variations between the patterns of steroid excretion in human urine in health and in disease, including neoplastic growth. The methods described include the procedures which have been standardized (a) for the collection, hydrolysis, and extraction of urine; (b) for the separation of the ether-soluble material into acidic, neutral, and phenolic fractions; (c) for the separation of the neutral fraction into ketonic, nonketonic alcoholic, and nonketonic nonalcoholic fractions; and (d) for the separation of the ketonic and of the nonketonic alcoholic fractions into the digitonin-precipitable and digitonin-nonprecipitable components. The method for the systematic chromatographic adsorption analysis of the ketonic fractions has been described. Examples of the results obtained by the application of these methods have been presented. It is concluded that the methods described are satisfactory for the separation and isolation of the constituents of the urinary steroid excretion patterns in health and in disease.—*Auth. Summ.*

Dobriner, Konrad [Sloan-Kettering Inst., New York City]; Lieberman, Seymour; Rhoads, C. P.; Jones, R. Norman; Williams, V. Z., & Barnes, R. Bowling: **Studies in steroid metabolism. III. The application of infra-red spectrometry to the fractionation of urinary ketosteroids.** J. Biol. Chem. 172: 297-311, Jan., 1948.—Methods of infrared spectrometry have been developed for the identification of the steroid metabolites found in urine. These methods can be applied both to the control of the fractionation procedures by which the individual steroid metabolites are separated and to the identification of the pure substances so obtained. The application of these methods to the estimation of the composition of binary mixtures of steroids, and to the detection of previously unrecognized steroid constituents in the sequence of components obtained by fractional chromatographic analysis are discussed.—*Auth. Summ.*

Elson, L. A., & Harris, R. J. C. [Roy. Cancer Hosp. (Free), London, Eng.]: **The influence of 1 : 2 : 5 : 6-dibenzanthracene on the nucleic acid content of the liver of rats maintained on high and low protein diets.** Brit. J. Cancer 1: 327-334, Sept., 1947.—The effect of the administration of 1 : 2 : 5 : 6-dibenzanthracene on the nucleic-acid balance in the livers of rats maintained on high and low protein diets has been investigated. The desoxypentosenucleic-acid concentration is decreased, and correspondingly there is an increase in the ratio of pentosenucleic to desoxypentosenucleic acid. The implications of this change are discussed in relation to the different growth-inhibitory activity of the carcinogen in animals maintained on diets of different protein content.—*Auth. Summ.*

Engel, R. W.; Copelnnd, D. H., & Salmon, W. D. [Alabama Polytech. Inst., Auburn, Ala.]: **Carcinogenic effects associated with diets deficient in choline and related nutrients.** Ann. New York Acad. Sc. 49 (1): 49-67, 1947.—Choline-deficient diets, of different composition from those previously used in this laboratory, were fed to rats for prolonged periods. Neoplasms of one or more types were observed in 14 out of 18 rats fed these diets for 5 to 11 mos. No neoplasms were observed in control animals fed the same diets supplemented with 0.2% choline chloride.—*Auth. Summ.*

Euler, H., v., & Hahn, L. [Univ. Stockholm, Sweden]: **Concentrations of ribonucleic acid and desoxyribonucleic acid in animal tissues.** Arch. Biochem. 17: 285-291, May, 1948.—The content of ribonucleic acid (RNA) and of desoxyribonucleic acid (DNA) in liver, spleen, and heart of normal and cancerous rats was determined. The ratio RNA/DNA was found for—normal rats: liver 2.4, spleen 0.5, heart 1.5; sarcoma-bearing rats: liver 2.8, spleen 0.5, heart 1.6. The difference of the ratios in liver, though distinct, cannot be regarded as significant.—*Auth. Summ.*

Frantz, Marthella; Kirschbaum, Arthur, & Casas, Carmen [Univ. Minnesota M. Sch., Minneapolis]: **Endocrine interrelationship and spontaneous tumors of the adrenal cortex in NH mice.** Proc. Soc. Exper. Biol. & Med. 66: 645-646, Dec., 1947.—The occurrence of spontaneous estrogen-secreting tumors of the adrenal cortex can be correlated with early cessation of ovarian activity in the NH stock. Estrogen is probably secreted by the adrenal cortex even preceding adenoma formation. Gonadotrophic hormone enhanced estrogenic secretory activity of cortical adenomas.—*Auth. Summ.*

Greenstein, Jesse P., & Leuthardt, Florence M. [Nat. Cancer Inst., Bethesda, Md.]: **Effect of added phosphate on glutamine desamidation**

in tumors. J. Nat. Cancer Inst. 8: 161-162, Feb., 1948.—Glutamine incubated with digests of primary rat hepatoma, transplanted mouse hepatoma, transplanted mouse sarcoma, transplanted mouse leukemia, transplanted mouse amelanotic melanoma, and transplanted mouse mammary tumor was more rapidly deamidated when phosphate was added to the digests. The more rapid deamidation indicates that these tumors possess a glutaminase of the liver rather than of the kidney type.—*Auth. Summ.*

Hoch-Ligeti, C. [London Hosp., Eng.]: Effect of feeding 7OH-2-acetaminofluorene to albino rats. Brit. J. Cancer 1: 391-396, Dec., 1947.—Fifteen out of 20 albino rats receiving 0.07% AAF developed tumors between the 183d and 461st day of the experiment. 7 out of 8 rats receiving 0.07% 7OH-2AAF for more than a yr. showed neoplastic changes, 1 after 380 days and the remainder at about the 700th day. 3 tumors were found in 17 control rats killed after 500 days.—*Auth. Summ.*

Kupperman, Herbert S., & Greenblatt, Robert B. [Univ. Georgia Sch. Med., Augusta]: The effect of steroid hormones on the carcinogenic activity of benzpyrene. Exper. Med. & Surg. 6: 156-166, May/Aug., 1948.—Observations on the combined administration of various steroid hormones and benzpyrene on the carcinogenic propensity of the latter compound [in white rats] are presented. Intra-uterine administration of pellets of the carcinogen alone and together with pellets of estradiol, progesterone, and testosterone failed to bring about neoplastic changes. The depressing effect of estradiol dipropionate on the growth of sarcomas induced by the subcutaneous administration of benzpyrene was accentuated by the additive effect of desoxycorticosterone acetate. Transplantation of the benzpyrene-induced sarcomas for 3 to 6 generations was influenced by the steroid hormones. Estradiol dipropionate not only inhibited the rate of growth of the transplanted sarcomas but also decreased the incidence of takes. On the other hand, progesterone, testosterone, and desoxycorticosterone appeared to enhance the growth of the transplanted sarcomas.—*Auth. Summ.*

Lansing, A. I.; Rosenthal, T. B., & Au, M. H. [Washington Univ. Sch. Med., St. Louis, Mo.]: Ultrafilterable and non-ultrafilterable calcium in normal, hyperplastic epidermis and squamous cell carcinoma. Arch. Biochem. 16: 361-365, Mar., 1948.—Ultrafiltration studies have been conducted on normal and hyperplastic epidermis and squamous-cell carcinoma. Ultrafilterable calcium of normal epidermis is 38% of total calcium. In methylcholanthrene-induced hyperplasia, the ultrafilterable calcium level is unaltered, but in squamous-cell carcinoma it is reduced to 29%.—*Auth. Summ.*

Lieberman, Seymour; Dobriner, Konrad; Hill, B. R.; Fieser, Louis F., & Rhoads, C. P. [Sloan-Kettering Inst., New York City, & Harvard Univ., Cambridge, Mass.]: Studies in steroid metabolism. II. Identification and characterization of ketosteroids isolated from urine of healthy and diseased persons. J. Biol. Chem. 172: 263-295, Jan., 1948.—The chemical characteristics of 35 α-ketosteroids and 7 β-ketosteroids that have been isolated from human urine are described. 26 of these 42 steroids have been completely identified. This group includes (a) 14 that have not been isolated previously from human urine, of which 10 are known compounds: etiocholanol-3α-one-17 acetate-3; $\Delta^{11(?)}$-androstenol-3α-one-17 acetate-3; androsterone acetate; allopregnanedione-3,20; pregnanedione-3,20; androstanedione-3,17; etiocholanedione-3,17; Δ^{4}-androstenedione-3,17; 17-isopregnanol-3α-one-20; and etiocholanol-3α-dione-11,17; and 4 are new steroids: Δ^{9}-etiocholenol-3α-one-17; pregnanediol-3α,17α-one-20; allopregnanediol-3α,6-one-20; and $\Delta^{2(\text{or }3)}$-allopregnenone-20; and (b) 12 that have been isolated before from human urine by other investigators: $\Delta^{3,5}$-androstadienone-17; $\Delta^{2(\text{or }3)}$-androstenone-17; 3-chloro-Δ^{5}-androstenone-17; allopregnanol-3α-one-20; pregnanol-3α-one-20; androsterone; Δ^{9}-androstenol-3α-one-17; etiocholanol-3α-one-17; androstanediol-3α, 11β-one-17; allopregnanol-3β-one-20; isoandrosterone; and dehydroisoandrosterone.

16 of these 42 steroids have been incompletely identified. This group includes 6 that have been characterized by melting point and C and H analysis, and 10 that were isolated in such small amounts that they have been characterized only by melting points. The sequence in which these steroids are eluted from aluminum-oxide and magnesium-silicate chromatographic columns is discussed; some general principles concerning the order of elution are presented. The relationships of the steroids isolated as metabolites in urine to the known and postulated precursors among the hormones are discussed; certain deductions concerning these relationships are given.—*Auth. Summ.*

Mayer, R. L. [Ciba Pharmaceut. Prod., Inc., Summit, N. J.]: Aromatic amines and azo-dyes in allergy and cancer. J. Invest. Dermat. 10: 389-396, May, 1948.

Meister, Alton, & Greenstein, Jesse P. [Nat. Cancer Inst., Bethesda, Md.] Dehydropeptidase activity of normal and pathological human sera. J. Nat. Cancer Inst. 8: 169-171, Feb., 1948.—The hydrolysis of the dehydropeptides, *dl*-alanyldehydroalanine and glycyldehydroalanine by normal and pathological human sera was investigated. Increased serum dehydropeptidase was found in patients with liver disease and occasionally in other disorders. [There was no appreciable difference between the serum dehydropeptidase activity of the sera of cancer patients and those of the noncancer group.]—*Auth. Summ.*

Miller, J. A. [Univ. Wisconsin M. Sch., Madison]: Studies on the mechanism of the effects of fats and other dietary factors on carcinogenesis by the azo dyes. Ann. New York Acad. Sc. 49 (1): 19-28, 1947.—It appears that the level of riboflavin in the liver of the rat is an

important factor in determining the probability that a given liver will develop a tumor when *p*-dimethylaminoazobenzene is fed in various diets. Since other workers have not found a similar effect with spontaneous mammary tumors or with tumors due to methylcholanthrene, it is possible that the action of riboflavin in counteracting carcinogenesis with this dye occurs prior to the carcinogenic process, e.g., through detoxication. However, enzymatic systems containing riboflavin may be involved directly in the carcinogenic process initiated by the dye. In any case, the effect of riboflavin should be a good tool in further attacks on the nature of this carcinogenic process.—*Auth. Summ.*

Morel, A.; Enselme, J.; Josserand, A.; Traeger, J., & Carraz, Y.: Les phosphatases et le tissu cancéreux. [Phosphatase and cancer tissue.] J. de méd. de Lyon 29: 81-87, Feb. 5, 1948.—Since phosphatases are increased in cancer tissue, and are indispensable factors in the emission of cellular energy and in the catabolism of biological molecules, is this phosphatase activity the cause of the great activity of cancer cells or the proof?—*M. C. J.*

Morris, Harold P. [Nat. Cancer Inst., Bethesda, Md.]: Effects on the genesis and growth of tumors associated with vitamin intake. Ann. New York Acad. Sc. 49 (1): 119-140, 1947.—Extreme deficiencies of pantothenic acid and riboflavin, produced rapidly during a short period of time, decreased the rate of growth of spontaneous mammary adenocarcinoma in strain C3H mice. On the other hand, the production of extreme deficiency of pyridoxine under similar experimental conditions did not affect the rate of growth of the mammary tumor. The rapid thiamine depletion of the mouse decreased the rate of growth of the spontaneous mammary tumor to the same extent as its food intake was voluntarily restricted. However, in paired tumor-bearing mice forcibly fed equal quantities of thiamine-deficient or thiamine-supplemented food, the average growth rate of the mammary tumors was depressed in the presence of added thiamine. The feeding of pyridoxine, thiamine, or riboflavin in amounts sufficient to maintain the body weight of the adult non-tumor-bearing animal also furnished a sufficient amount of these vitamins to eliminate any effect on the growth rate of the tumors. Riboflavin supplementation resulted in increasing the number of tumors which developed. The riboflavin supplementation prior to the appearance of the 1st tumor, however, was no more effective than giving the supplement after the tumor appeared. The production of partial riboflavin deficiency by feeding amounts of riboflavin just sufficient to prevent clinical ariboflavinosis depressed the average body weight about 30%, prevented full development of the mammary glands, and reduced the tumor incidence of the partially deficient mice to ⅔ that of the controls. Some possible explanations of the effects on tumor genesis and growth due to deficiencies of different vitamins have been discussed. It was pointed out that the possible relation of thiamine intake to inactivation of estrogen in the body needs to be further investigated to see if an estimation of thiamine deficiency can be a useful criterion for detecting a potential uterine cancer-producing condition prior to the appearance of the cancer at that specific site.—*Auth. Summ.*

Peterminn, Mary L., & Hogness, Katharine R. [Sloan-Kettering Inst., New York City]; Electrophoretic studies on the plasma proteins of patients with neoplastic disease. I. Gastric cancer. II. An acid protein present in the plasma. Cancer 1: 100-103; 104-108, May, 1948.

Petermann, Mary L.: Karnofsky, David A., & Hogness, Katharine R. [Sloan-Kettering Inst., New York City]: Electrophoretic studies on the plasma protrins of patients with neoplastic disease. III. Lymphomas and leukemia. Cancer 1: 109-119, May, 1948.

Rondoni, Pietro & Boretti, Giulia [Inst. Naz. Studio e Cura dei Tumori, Milan, Italy]: Gruppi sulfidrilici e cancerogenesi chimica. [The sulfhydryl group and chemical cancerigenesis.] Tumori 21 (4/5): 274-278, 1947.

Ruddy, M. Veronita [Inst. Divi Thomae, River Forest, Ill.]: Effect of hydrogen ion concentration on oxygen consumption of carcinoma 1509la from ABC and dba mice. Stud. Inst. Div. Thom. 5: 27-33, 1946-1947.

Rusch, H. P., & Miller, J. A. [Univ. Wisconsin M. Sch., Madison]: Demethylation of carcinogenic aminoazo dyes by autoxidizing linoleic acid. Proc. Soc. Exper. Biol. & Med. 68: 140-143, May, 1948.

Waterman, N.: Berkhout, H. W., & Bos, C. J.: Investigations into the biological significance of amino acids on malignancy. Enzymologia 12: 206-220, Nov. 20, 1947.—Normal, embryonic, and tumor tissues were subjected to the action of a spleen extract. [Tumor tissues: T 86157; T 86197; T 90504; T 90904; spontaneous leukosis; breast carcinoma; carcinoma M 63; carcinoma of lung; tar sarcoma; tar carcinoma, sarcoma N.G. 35.] Normal tissues respond to the addition of this extract to the medium with an important increase of consumption of oxygen (30-70%+). The Warburg technique was used throughout. Tumor tissue shows, as a rule, a far smaller response to the addition of this extract, the increase not surpassing 10-20%. Different tumors behave extremely differently in this respect and this individual behavior is constant in every kind of tumor. The basal consumption of oxygen is also very variable; normal as well as low figures may be found. Embryonic tissues do react in a variable way, which depends greatly upon the age of the embryo. As a rule they respond to the addition of spleen extract: the basal uptake of O_2 is not very high, generally below that of liver or kidney tissue. In the early stages of development, reaction towards the addition of unnatural glutamic acid was observed. Tissues of animals inoculated with tumor show often the "torpidity" against addition of extract which, as a rule, is shown by tumor tissue itself. This is

correlated with the spreading of tumor cells through the organism. The action of the extract must be ascribed chiefly, in any case, to the amino acids it contains. Demonstrated and determined were: glutamic acid, glycine, aspartic acid, and tryptophane. The presence of proline is highly probable. The methods of quantitative determination are described in detail. The action of 24 amino acids and some related compounds upon respiration was tested. Among the amino acids: proline, (l+) glutamic acid, glycine, aspartic acid, and tryptophane are the most active. Interesting is the inactivity of oxyproline compared with proline. Of particular interest is the activity of sarcosin and (less) of betainehloride. The response was studied toward (d—) and (l+) glutamic acid. It was found that normal adult liver tissue never reacts with the (d—) form, but that tumor tissue occasionally does so. Young embryonic tissue may react also on addition of the unnatural form. The conclusion may be drawn that in young embryonic tissue, as well as in some kinds of tumor tissue, there exists still an enzyme system not as yet differentiated as to optical isomerism. But this is not a law of strict validity. In any case, there is still certainly room for Koegl's conception. Very surprising is the frequency of the reactivity to the unnatural (d+) form by "normal" kidney tissue. A tentative explanation is discussed. The results of this work are, in a general way, in concordance with the outcome of recent investigations on the biology of amino acids. In the light of our investigations, the individuality of all tumor forms should again be emphasized.—*Auth. Summ. & Concl.*

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pyrene per dose, only 1 developed a sarcoma after 5 mos. 1 tumor arose in a series of 20 mice injected twice weekly for 32 wks. with a solution of tetramethyluric acid containing 10 μg. benzpyrene per injection. The results have been discussed.—*Auth. Summ.*

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ACTH- AND CORTISONE-INDUCED REGRESSION OF LYMPHOID TUMORS IN MAN

A Preliminary Report

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THIS study was undertaken to determine whether the rate of growth of various types of neoplastic tissues in man would be influenced by increasing adrenal cortical function. Adrenal cortical hyperfunction as manifested in patients with Cushing's syndrome is associated with a loss of body protoplasm. Albright has interpreted this to be the result of an inability to synthesize tissue rather than to an increased rate of tissue destruction. Malignant lymphoid tumors were selected for study because Dougherty and White had observed that increased adrenal cortical function in animals resulted in involution of normal lymphoid tissues; and Heilman and Kendall, that administration of Compound E resulted in regression of a lymphoid tumor in mice. Studies of Dobriner, Lieberman, and Rhoads [2–4] on the excretion of urinary steroids in patients with cancer including lymphoid neoplasms, revealed changes indicative of altered adrenal cortical function, and these findings suggested that administration of adrenal cortical hormones or stimulation of adrenal cortical function by adrenocorticotropic hormone might influence the course of the disease.

Clinical and metabolic observations were made on seven patients who received adrenocorticotropic hormone (ACTH*): three with chronic lymphatic leukemia, and one each with follicular lymphosarcoma, Hodgkin's disease, carcinoma of the prostate, and metastatic carcinoma of the breast; and one with chronic lymphatic leukemia who received cortisone acetate.† Two patients, one with Hodgkin's disease, the other with metastatic carcinoma of the breast, were women. ACTH and cortisone acetate were administered in a dosage of 100 to 200 mg. daily in four divided doses for periods of eighteen to thirty days (ACTH dosage equivalent to Armour Standard LA-1-A).

In the six patients with lymphomatous tumors, there was a dramatic and progressive decrease in the size of enlarged lymph nodes and of enlarged spleens during the administration of ACTH or cortisone acetate. Definite involution of lymphoid masses was first apparent after three days of administration of ACTH and after six days of cortisone acetate. In the two patients with carcinoma, there was no obvious change in the clinical course of the disease during or after giving ACTH.

Of the six patients with lymphoma, two (lymphatic leukemia and lymphosarcoma) have shown no evidence of regrowth of abnormal masses within the period of ten weeks of observation that has elapsed since ACTH was discontinued. In the patient with Hodgkin's disease, enlargement of lymph nodes occurred within six weeks after stopping ACTH, although other lymph nodes that

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† Cortisone is the name given by Kendall to 17-hydroxy-11-dehydrocorticosterone (Compound E, Kendall).

had previously disappeared have not reappeared during ten weeks of observation. One patient with lymphatic leukemia showed no obvious regrowth of lymph nodes for a period of six weeks after stopping cortisone acetate. During the subsequent four weeks, however, marked enlargement of the lymph nodes and of the spleen occurred. This patient is receiving ACTH at present, and involution of the lymphoid masses and spleen has occurred for a second time. Another with lymphatic leukemia showed rapid enlargement of the lymph nodes and spleen within a few days after stopping ACTH. After an interval of ten weeks, he is now receiving cortisone acetate, and involution of lymphoid masses has again occurred. This patient will be discussed in more detail later. The third with lymphatic leukemia died of intercurrent infection (hemorrhagic chickenpox and bronchopneumonia) two weeks after ACTH was stopped. In this patient, one lymph node enlarged rapidly within the first week after stopping ACTH.

None of this group of patients was critically ill at the time these studies were started. All noted an increasing sense of well-being during the first two weeks of administration of ACTH or cortisone acetate, together with an increase in appetite, which developed during the first week. In three patients, hunger became a major complaint. After two weeks, all of the patients noted muscular weakness that varied from mild to severe. During the experimental period, all of the patients retained fluid and developed peripheral edema. Within twenty-four to forty-eight hours after discontinuing the hormones, a marked diuresis occurred, and the peripheral edema rapidly disappeared. In one woman, a severe acneform eruption developed on the face, arms, and trunk, which persisted for several weeks after ACTH was stopped. This patient also had an increase in growth of facial hair, but no other signs of virilism were noted. In one patient with lymphatic leukemia, a first attack of gout appeared two weeks after discontinuing ACTH.

In the four patients with lymphatic leukemia, there was a marked rise in the white blood-cell count during the experimental periods. The initial white counts ranged from 250,000 to 750,000 with approximately 98 per cent mature lymphocytes. After about twelve days of ACTH or cortisone acetate administration, the counts reached a peak ranging from 500,000 to 1,250,000 with no change in the differential count. During the remainder of the experimental period, the white counts receded toward the initial level. After ACTH or cortisone acetate was discontinued, there was a progressive fall in the white-cell count to levels of 60,000 to 500,000, which was below the initial level in all cases. In none of the patients who received ACTH was there a marked change in the red blood-cell count or hemoglobin level. In the patient who received cortisone acetate, there was a progressive fall in both throughout the period of study, and he required transfusions three weeks after cortisone acetate was discontinued.

Usually serum chloride and potassium levels decreased and the serum *p*H and bicarbonate rose in the patients who received ACTH. In three patients, the serum potassium fell to abnormal levels and characteristic electrocardiographic changes of potassium deficit developed. The muscular weakness noted by these patients was probably related to the electrolyte disturbances.[8] All showed a fall in the total serum proteins during the experimental period. In most of these, there was a tendency for the serum phosphorus to fall and for the fasting blood sugar to rise while ACTH was being given. Glycosuria did not appear in any. A slight decrease in the total serum cholesterol and in the cholesterol-ester fraction was observed in the four patients in whom these measurements were made.

During the experimental period, all patients exhibited a negative potassium, phosphorus, nitrogen, and calcium balance, and a positive sodium and chloride balance. In the six with lymphomatous lesions, the excretion of phosphorus during the administration of ACTH or cortisone acetate was greater than the phosphorus excretion calculated from the actual nitrogen and calcium excretion, using the accepted ratios for N to P in protoplasm and Ca to P in bone.[9] Chemical analysis of

fat-free muscle and tumor tissue from two patients with lymphatic leukemia and one with follicular lymphosarcoma revealed 2.9 times as much phosphorus per unit of nitrogen in tumor tissue as in muscle. These data provide evidence that tumor tissue was actually destroyed in this group of patients.

In one patient with lymphatic leukemia, the dietary intake was doubled after eighteen days of ACTH administration, and ACTH continued for an additional twelve days. This increase in diet was associated with a sudden shift from a negative to a positive nitrogen balance. When ACTH was stopped, there was a rapid increase in the size of the lymphoid masses as well as in the spleen. These data indicate that the metabolic response induced by ACTH may be altered by the dietary intake and appear analogous to the results of similar experiments by Ingle in rats.

The excretion of ketosteroids and reducing steroids was increased in all patients during the administration of ACTH. There was considerable individual variation in the extent of this steroid increase, and in two patients, a significant increase was observed only after the dosage of ACTH was increased from 100 to 200 mg. per day.

Histological examination of lymph nodes before and after ACTH or cortisone acetate administration, made in two patients with lymphatic leukemia, showed no definite change in the histological picture of the nodes. In the lymph node obtained from the patient with lymphosarcoma, germinal centers disappeared and cellularity decreased following ACTH administration.

In none of the patients studied has a complete clinical remission of the disease been obtained. These observations were designed to be short-term metabolic studies to determine whether alteration in adrenal cortical function would affect the rate of growth of tumors. Although no obvious clinical response was observed in the two patients with carcinoma, it cannot be concluded that ACTH administration was entirely without effect on the growth of these tumors; assessment of such tumor growth could only be made by indirect means. The possible role of ACTH and cortisone acetate as therapeutic agents in patients with lymphomatous tumors has not been established by these studies. Whether complete clinical remissions can be obtained by more prolonged administration of these hormones remains to be determined. It is of interest that two patients with lymphatic leukemia have shown a second response to the administration of ACTH or cortisone acetate indicating that tumor resistance has not yet developed to these agents.

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GENESIS OF ENDOMETRIAL CARCINOMA

*I. Study of Prior Biopsies**

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DESPITE numerous pathological studies of endometrial carcinoma during the past fifty years and investigations of large numbers of such cases statistically, the developmental stages of cancer of the uterine fundus are still controversial. In a recent excellent article by Speert,[24] it is pointed out that agreement is lacking as to whether endometrial hyperplasia leads to carcinoma. This may be ascribed in part to uncertain criteria for recognition of endometrial hyperplasia or early carcinoma. Also, previous endometrial biopsies are not often available in patients with advanced carcinoma. Several cases have been reported in which endometrial hyperplasia was diagnosed from three to six or more years before carcinoma was discovered,[3, 6, 12, 16, 24] but the total number of such examples is small and subject to rather wide variations in individual pathological interpretations.

Because of the importance to the patient of early diagnosis of irreversible endometrial neoplasia and the theoretical value of a better understanding of the histogenesis of endometrial carcinoma, it was considered desirable to search systematically for cases offering pertinent information. A group of 500 cases of endometrial cancer from the 1903 to 1948 records of the Free Hospital for Women was analyzed. From these, a group of 389 intensively studied cases, seen during the twenty-year period, 1929 through 1948, yielded 140 cases in which there had been a curettage or other pelvic operation one year or more before the first pathological diagnosis of carcinoma. It was possible to review the original histological preparations from sixty-seven cases.‡ Of these, thirty-five cases were rejected because of insufficient material, controversial diagnoses including possible endocervical adenocarcinoma or ovarian carcinomas with extension or metastasis to the uterus, or doubt as to the primary site of the carcinoma. Thirty-two cases remained in which it was possible to observe the endometrium from one to twenty-three years before invasive carcinoma was diagnosed. From one to six endometrial specimens were available from individual patients.

BIOPSY STUDY

Negative Endometrium. In seven instances with an interval of fifteen to twenty-three years between the curettage or biopsy and the diagnosis of carcinoma, the endometrium was essentially negative. Normal cyclic variations were present, three in proliferative and four in secretory phases of the intermenstrual period. One specimen showed slight adenomatous hyperplasia (which will be defined later), but in an effort to avoid vagueness, slight changes were not given consideration in this study.

It will be seen from Table 1 that an endometrial biopsy that did not exhibit hyperplasia was found in only five of forty specimens obtained one to thirteen years before recognition of cancer. Of these five, one showed chronic endometritis and two squamous metaplasia. Neither of the latter developed adenoacanthoma. No other examples of endometritis or metaplasia were encountered. These findings are taken to show that no endometrial abnormalities are to be expected,[22] fifteen or more years before cancer develops,

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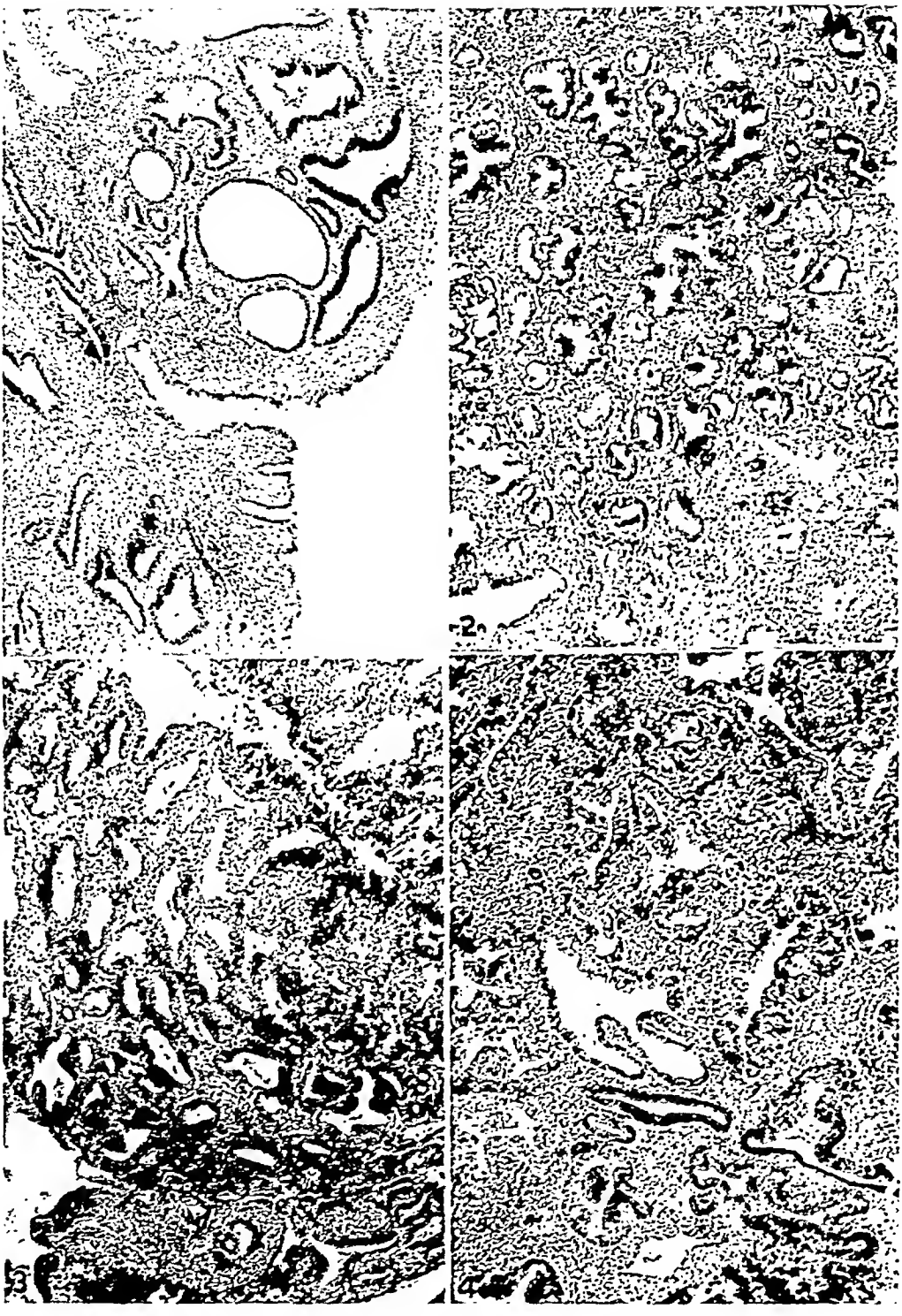

FIG. 1. *Portion of endometrial polyp with cystic hyperplasia. Patient aged 26 years. C.H. S-32-255. (H. & E. × 100.)* FIG. 2. *Another polyp, showing adenomatous hyperplasia with outpouchings of glands. Same patient, aged 30 years. B.H. S-36-195. (E.M.B. × 100.)* FIG. 3. *Curettings with transition from wide-spaced normal glands, to anaplastic changes, and close-packed glands with large eosinophilic cells diagnostic of carcinoma in situ. Same patient, aged 31 years. B.H. S-37-687. (E.M.B. × 100.)* FIG. 4. *Typical invasive endometrial adenocarcinoma, Grade II, from hysterectomy specimen. Same patient, aged 39 years. F.H.W. S-48-2480. (H. & E. × 100.)*

TABLE 1

ENDOMETRIAL FINDINGS PRIOR TO DIAGNOSIS OF CARCINOMA

In 32 Patients

Interval yrs.	*Cases biop.*	*No. biop.*	*Neg. or no hyperplasia*	*Polyp*	*Hyperplasia*			*Anaplasia*	*Carcinoma*		
					Infolding	*Cystic*	*Adenom.*		*In situ*	*Borderline*	*Invasive*
15-23	6	7	7	0	2	0	0	0	0	0	0
10-13	8	8	0	3	0	6	4	2	1	1	0
6-9	13	18	2	5	2	7	6	4	1	0	0
3-5	10	11	3	2	1	4	7	5	3	1	1
1-2	3	3	0	0	1	0	2	2	1	0	1
TOTAL	40*	47†	12	10	6	17	19	13	6	2	2‡

* Discrepancy due to patients with multiple biopsies.
† Discrepancy due to multiple biopsies in same time interval.
‡ Diagnostic errors.

but that within a prodromal period shorter than fifteen years, patients destined to develop cancer will usually possess recognizable hyperplastic endometrial alterations.

Polyps. Endometrial polyps were encountered in ten cases of this group. They also accompanied forty-six (12 per cent) of the 389 cases of carcinoma intensively investigated. Polyps are recognized in curettings by the presence of superficial epithelium on three sides of a rounded fragment, the glands of which have an irregular pattern, often with cystic hyperplasia or dilatation (Fig. 1). They were most frequently found (Table 1) six to thirteen years before the diagnosis of cancer was made, and thereafter progressively less often. In three cases, suspicious epithelial activity of types to be described occurred in polyps. Endometrial polyps are more frequent precursors of cancer than cervical polyps.[18] Except in women first biopsied after the menopause, benign endometrial polyps were less common preceding carcinoma than were generalized types of hyperplasia, in this small series. In the menopausal group as a whole, however, a generalized endometrial hyperplasia would often be considered an indication for prompt hysterectomy, hence no opportunity would be allowed for cancer to develop.

Focal Hyperplasia. The focal infolding of endometrial gland linings, encountered so frequently in otherwise negative biopsies taken to investigate sterility, is of dubious importance. It was observed six times in the thirty-two cases and bore no definite time relation to the development of cancer. Because it is more commonly seen in curettings than in endomyometrial blocks, some of the infoldings may be artifacts, produced by inversions of endometrial glands that have been pulled out intact by the curette. It may be termed "focal hyperplasia" or "infolding" as one prefers.

Generalized Hyperplasia. CYSTIC ENDOMETRIAL HYPERPLASIA. This is the best-known and most thoroughly studied type of change encountered. The glands are irregularly or spherically dilated, partly filled with secretion, and lined by high cuboidal or columnar epithelium showing evidence of proliferation by cell crowding or mitoses. One should avoid confusing cystic hyperplasia with endometrial glands mechanically obstructed and thereafter cystically dilated, as in the formation of cervical nabothian cysts. Seventeen examples of cystic hyperplasia were found among the thirty-two cases. The highest incidence was in the period six to thirteen years before carcinoma was discovered, when three quarters of the biopsies showed this change, but in the three- to five-year period it was still relatively common (Table 1). This is believed to indicate, as has been claimed,[2] that cystic hyperplasia is a rather frequent and important precursor of endometrial carcinoma. However, it should be noted that, in this small series, its relative incidence declines steadily from ten or more years before cancer to a year or two before. Study of cases with numerous

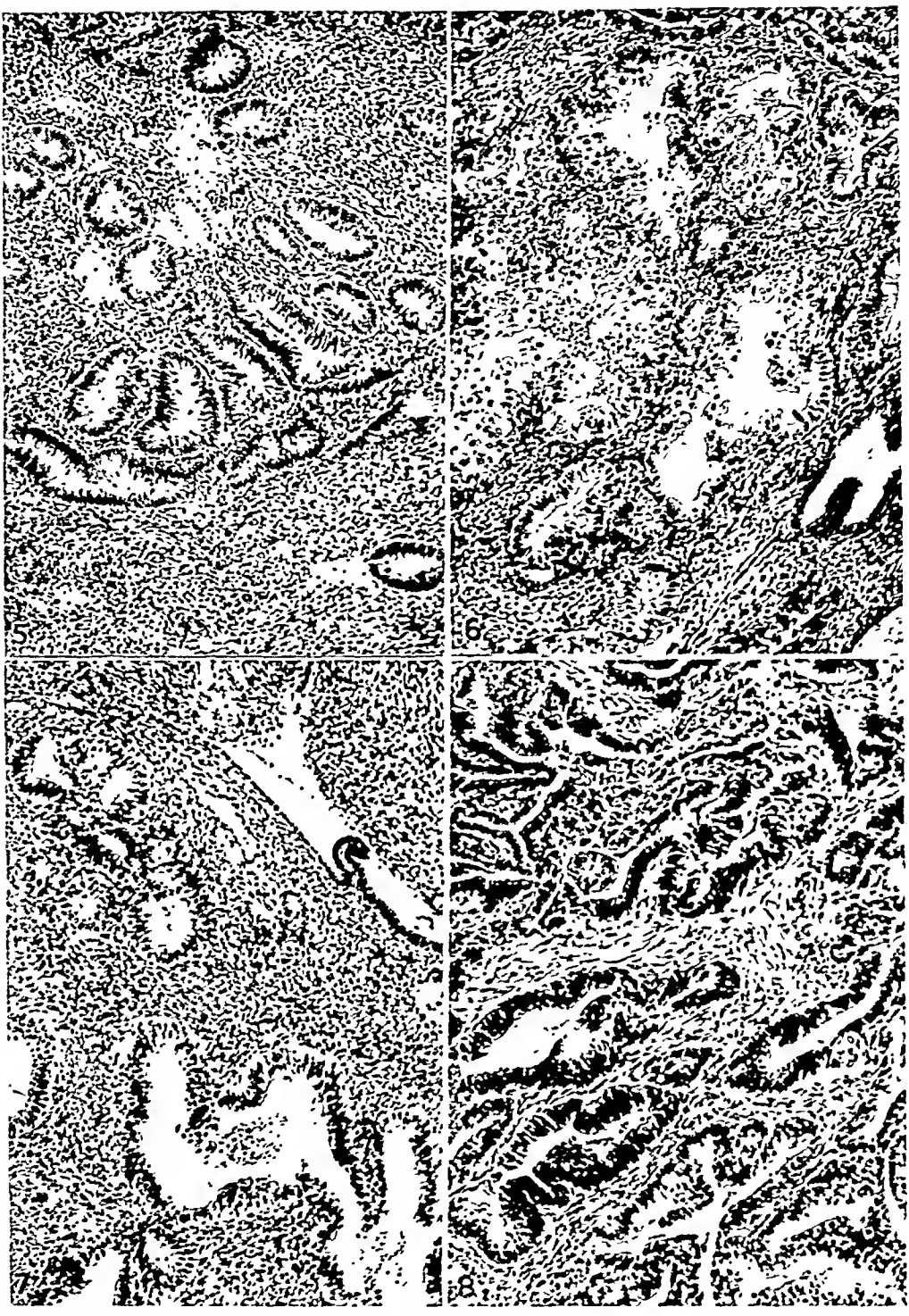

FIG. 5. *Portion of curettings showing endometrial hyperplasia and anaplasia. Patient, aged 54 years, also had an endometrial polyp removed, and 1500 mg.-hr. of radium administered at this time. F.H.W. 23051. (H. & E. × 100.)* FIG. 6. *Typical endometrial adenocarcinoma. Grade II, from hysterectomy specimen. Same patient as Fig. 5 but nine years later, at age 63. F. H.W. S-43-2369. (H. & E. × 100.)* FIG. 7. *Adenomatous hyperplasia and anaplasia of endometrium. From another patient, aged 61 years, to whom 2000 mg.-hr. of radium was administered after curettage. F.H.W. S-40-1865. (H. & E. × 100.)* FIG. 8. *Adenocarcinoma, Grade II, of endometrium with slight squamous metaplasia, metastasized and proved fatal. Same patient as Fig. 7 four years later, at age 65. F.H.W. S-44-1779. (H. & E. × 100.)*

sequential biopsies confirms the belief that cystic hyperplasia tends to be a remote rather than immediate forerunner of carcinoma.

ADENOMATOUS HYPERPLASIA. Adenomatous hyperplasia[8] of the endometrium was observed in nineteen of the thirty-two cases, the most frequent single endometrial abnormality found. By this is meant the outpouching of budlike, glandular projections into the supporting endometrial stroma (Fig. 2). At first, the small processes are connected with the parent gland like glove fingers, but eventually they may become pinched off with resultant groups of small, closely packed glands, some of which lie back to back (Fig. 7). The growth potential, instead of being directed outward into the uterine cavity with polyp formation, proceeds by introversion into endometrial stroma. Adenomatous hyperplasia occurred in every group from one to thirteen years before the diagnosis of carcinoma and was relatively most common in the period from one to five years before cancer. Of the various processes preceding endometrial carcinoma, it was both most often observed and found to show the most definite trend to increasing incidence as cancer approached.

ANAPLASIA. Anaplasia of endometrial epithelial cells occurred in thirteen of the biopsied cases. Dedifferentiation, or anaplasia, is shown by glandular lining cells that vary abnormally in size, shape, cytoplasmic staining, and polarity. Their nuclei are of irregular shape, size, and staining qualities (Fig. 5). While anaplasia is one facet of neoplasia, it is also encountered alone or as part of endometrial hyperplasia. In this series, anaplasia showed a trend to increasing frequency as cancer approached, similar to that of adenomatous hyperplasia (Table I).

It must be emphasized that none of the changes described so far, either alone or together, is considered evidence of irreversible neoplasia. Many patients with cystic or adenomatous hyperplasia, anaplasia, polyps, and infolding have been followed for years without development of carcinoma. Our material does not yet permit a definite statement as to how frequently each type of endometrial abnormality develops into carcinoma. This problem is being studied separately. However, in both investigations, adenomatous hyperplasia is proving to be the most sinister in prognosis. Individual cases have been encountered, on the other hand, in which all of the above types of hyperplasia and anaplasia were replaced by negative endometrium following establishment of ovulation in premenopausal patients, or gave way to senescent endometrium in the older age group

Carcinoma. The earliest stage of endometrial carcinoma observed—which is not invasive—is termed "carcinoma in situ." For approximately ten years in this laboratory, this diagnosis has been based upon the presence of endometrial glands composed of large cosinophilic cells with abundant cytoplasm. The nuclei tend to be pale with small chromatin granules and slightly irregular, folded, or scalloped nuclear membranes. Cytological anaplasia is present, but there is no stromal invasion (Fig. 3). The region of carcinoma in situ is usually focal and contrasts sharply in morphology and staining with neighboring unaffected glands. These observations are identical with those described and illustrated by Cullen[4] fifty years ago as an accompaniment of endometrial cancer and more recently referred to by Lahm[13] and others.[1 8 19 24] It has usually been termed "atypical hyperplasia"

The interpretation of these glandular changes as carcinoma in situ is based on study of a group of similar cases being reported separately. It may be stated in brief that endometrium with this microscopic picture does not revert to normal, hyperplastic, or senescent endometrium, and that unless completely removed or destroyed, it is followed in time by invasive endometrial carcinoma. Six specimens in the present series showed carcinoma in situ, from one to eleven years before the diagnosis of invasive carcinoma. The highest incidence was noted in the three- to five-year period before invasive cancer. Statistical data indicate an average eight-year–time interval between in situ and invasive endometrial cancer. No case was included in the present series that did not ultimately present clear-

cut invasive carcinoma, and in our statistics endometrial carcinoma in situ has not been classed with invasive cancer. This has been done to avoid possible confusion or error, and to permit critical examination of the concept by others.

Occasional endometrial curettings show anaplasia and questionable stromal invasion, changes that are on the borderline between hyperplasia, anaplasia, and carcinoma, and provoke controversy among different observers. No case, the final histological material of which was of this type, was included among the thirty-two cases reported, but earlier biopsies in two of these patients were examples of borderline invasive carcinoma. One of them, who had such regions in a polyp, did not develop invasive carcinoma until ten years later. If regarded as "adenoma malignum," its emergence as invasive adenocarcinoma represents the slowest change in behavior and type of cancer observed in this study. In contrast, the shortest interval found between a negative endometrial biopsy and carcinoma was three years.

Review of the patients with multiple biopsies showed that in two, invasive adenocarcinoma had been present for from one to five years before it was recognized. These represent diagnostic errors, ascribable to different criteria of malignancy used by different pathologists. It is additional evidence of the teaching that endometrial carcinoma must invade its stroma before penetrating into myometrium, and that stromal invasion may be relatively slow. This factor is one important reason for the relatively lower mortality of endometrial carcinoma, as contrasted with that of carcinoma of the cervix or breast.

Statistics of Biopsy Cases

Comparison of the ages of the thirty-two cases in the biopsy series with the whole series of 500 cases reviewed (Table 2) shows comparable age ranges in both groups, although there is a disproportionate representation of premenopausal cases in the small series. Follow-up study of the thirty-two biopsy cases indicates that seven patients are living but have been followed less than five years after the diagnosis of carcinoma. Of the remaining twenty-five, eight have had a recurrence or died of cancer, and three others have died ostensibly from cardiovascular disease. The gross five-year mortality is thus 44 per cent for the biopsy series, compared with 44.3 per cent reported for all endometrial cancer at the same hospital. This is confirmatory evidence of the invasive nature of the endometrial carcinoma that finally developed among the thirty-two cases (Figs. 4, 6, 8).

Table 2

AGE INCIDENCE OF 500 CASES OF ENDOMETRIAL CARCINOMA (1903-1948) COMPARED WITH 32 CASES OF THE BIOPSY SERIES

Age, yrs.	*Cases, whole series*	*Cases, biopsy series*
25-30	3	3
31-35	4	1
36-40	7	3
41-45	36	4
46-50	60	4
51-55	100	6
56-60	103	4
61-65	88	5
66-70	53	1
71-75	29	1
76-80	13	0
81-88	4	0
Total	500	32

In collecting cases with prior biopsies, there will be a natural selection of those patients who have had clinical difficulties such as menometrorrhagia, sterility, or amenorrhea. The incidence of metrorrhagia prior to the diagnosis of cancer has been estimated at up to 90 per cent with an average eighteen months' duration, and it is not certain how often it is observed for longer periods. Childless women are more frequent in the endometrial cancer series than in the population, but many are unmarried. Cases like the eleven premenopausal women (Jones and Brewer) with coexistent carcinoma and normal endometrial cyclic changes would not seem likely to be included in a group of cancer patients with earlier biopsy studies.

In summary, it would not be justifiable to generalize from our small series that all persons destined to have endometrial carcinomas sequentially develop polyps, cystic hyperplasia, then adenomatous hyperplasia, anaplasia,

and finally carcinoma in situ followed by invasion. These observations merely include some cases in which this was observed, and a group that, as a whole, suggests that such progressive stages not infrequently lead to carcinoma. Other routes to cancer formation doubtless exist.

Exogenous Factors

Radiation. Ionizing radiation therapy is an extrinsic influence of increasing importance in recent studies of development of endometrial carcinoma.[3, 22, 25] It was used in treating benign conditions of the uterus in twenty of the thirty-two cases. Radium dosages employed varied from 400 mg.-hr. given eight years before the diagnosis of cancer to 2400 mg.-hr. five years before cancer. The average radium dose was 1270 mg.-hr. administered an average of seven years before recognition of cancer in the thirteen cases on which data are complete. Roentgen-ray therapy was given one patient, 550 r eight years before cancer. Other dosages are unknown. Perhaps one should interpolate, for these twenty cases, a stage of radiation reaction of endometrium five to eight years before cancer was found. These cases, together with other information from this clinic and recent publications, tend to show that radiation therapy of the uterus for benign conditions is followed by a greater than expected incidence of endometrial carcinoma. The unusual incidence of carcinosarcoma following radiation is confirmed in our material, for three of the twenty cases irradiated had carcinosarcoma. Other histological diagnoses in the biopsy series were twenty-six adenocarcinomas and three adenoacanthomas.

Hormones. Estrogen therapy, particularly stilbestrol, has been suggested as the cause of several endometrial carcinomas.[5, 6, 8, 26] No case in the biopsy series could be ascribed to administered estrogens, although six of the 389 intensively studied cases of endometrial cancer had received significant amounts of stilbestrol. In addition, seven of these cases were associated with granulosa-cell tumors or thecomas of the ovary. Five of the six stilbestrol-treated patients had received from 80 mg. in the course of twenty-one months to 360 mg. in twelve months and had a polypoid or generalized endometrial hyperplasia. Only two patients, 50 and 78 years old, who received the larger doses were regarded as examples of adenocarcinoma possibly attributable in part to stilbestrol. Polyps were frequently encountered by-products of estrogenic stimuli. Secretory activity is relatively frequent in the fundus cancers influenced by endogenous hormones from ovarian tumors. Thus, in four of the seven cases with estrogenic ovarian tumors, the carcinoma showed subnuclear vacuolization. None of the stilbestrol-treated cases showed secretory carcinoma.

In contrast, three patients in the 500-case series developed endometrial cancer up to thirty years after castration, as previously reported by Smith.[23] The frequently repeated statement that castrates never develop endometrial cancer may be rebutted by asking whether there are significant numbers of women whose ovaries have been removed but who retain the uterus.

Statistical Information

Statistical investigation of the 500 endometrial carcinomas, already referred to, may provide supplementary information concerning the genesis of this tumor. The age incidence shown in Table 2 closely corresponds with several other series.[9, 15, 18, 24] The mean age is 57.2 years. Seven cases less than 36 years of age are included, and because they show conditions somewhat different from older patients, they are being reported separately with eight cases of similar age seen in consultation. In the whole series are included six cases in colored women. No definite racial preponderance was noted among the other patients.

A more detailed analysis was possible in 389 cases seen from 1929 to 1948, since the data were more fully recorded. Of these, 264 (68 per cent) were postmenopausal, eighty-nine (23 per cent) were menstruating, and the remainder (9 per cent) menopausal or indeterminate. The average age at the menopause was 47 years. Eighty-five cases were in un-

TABLE 3

INTERVAL BETWEEN LAST CHILDBIRTH AND DIAGNOSIS OF CARCINOMA IN 182 CASES

Interval, yrs.	*No. cases*
4 to 10	12
10 to 20	44
20 to 30	67
30 to 40	43
40 to 54	16

married women, and an additional sixty-seven had been married more than five years but were childless; in all, 152 (39 per cent) were never pregnant. A family history of cancer was elicited in forty-eight (12 per cent); of diabetes mellitus, in twenty-five (6 per cent); of tuberculosis, in thirty-five (9 per cent); and of cardiovascular-renal disease, in sixty-six (17 per cent). Five patients with endometrial cancer had previously had breast operations, and twelve, thyroidectomies. In 182 patients with children, cancer occurred from four to fifty-four years after the last childbirth, with peak incidence at twenty-six years postpartum (Table 3).

Obesity was noted in 170 cases (44 per cent). Diabetes mellitus was diagnosed in thirty-three (9 per cent), an incidence similar to that reported in other studies.[16, 17, 20] In comparable age groups in the population, 34 per cent weigh more than 160 pounds, and in different series 1.3 to 6.9 per cent of women this age have diabetes.* Many patients also had hypertension or arthritis.[23] The relationship between endometrial carcinoma, obesity, hypertension, arthritis, and diabetes mellitus is as yet obscure, but hints at a common metabolic disorder. Forty-five patients (12 per cent) had other primary malignant tumors of which thirteen were carcinoma of the ovary, thirteen of the stomach or intestine, ten of the breast, six of the cervix, and three elsewhere. Many of these cancers occurred years after the endometrial carcinoma.

* We are indebted to Mr. Herbert H. Marks of the Metropolitan Life Insurance Company, New York, for providing the incidence of obesity and diabetes in women 50 to 59 years, from sources including the Statistical Bulletin and surveys of the U. S. Public Health Service.

Histological diagnoses of the endometrial carcinomas were as follows: adenocarcinoma, 333 (86 per cent); adenoacanthoma, fifty-one (13 per cent); carcinosarcoma, four (1 per cent); and squamous carcinoma, one case. Accompanying benign ovarian tumors included twelve serous and three pseudomucinous cystadenomas, six cystadenofibromas, and three fibromas. Among other ovarian neoplasms, seven granulosa-cell tumors, three with thecomatous areas, have already been mentioned.

Leiomyomas of the uterus accompanied carcinoma in 38 per cent of 319 uteri examined, and adenomyosis was present in an additional 7 per cent. Of 273 cervices examined microscopically, 75 per cent had only chronic cervicitis, with additional squamous metaplasia in 11 per cent, epidermidization of cervical glands in 5 per cent, and cervical polyps in 9 per cent.

For the entire group, a verified mortality of 34 per cent was due to cancer, an additional 7 per cent mortality to cardiovascular disease, and 3 per cent to miscellaneous other causes, making a total gross mortality of 44 per cent at the five-year follow-up period.

DISCUSSION

Advantage may be taken of endometrial biopsies to study the development of endometrial carcinoma. The knowledge thus gained and supported by statistical data, if properly interpreted, should advance understanding of this neoplasm. The presented data support the studies of others in showing that endometrial cancer is seen in women at a mean age of 56 to 57 years, but either premenopausal or postmenopausal, and that it is more common in nulliparous, obese, or diabetic women than would be expected. Biopsy studies indicate a tendency to endometrial polyps and cystic hyperplasia, most marked six to thirteen years before recognition of cancer. It has been well established clinically and experimentally that these are tissue effects of excess estrogen stimulation. At 40 to 50 years, ovulatory cycles and fertility decline, and uninterrupted or unopposed estrogen activity becomes more common. Ovarian cysts, twice as common

with endometrial cancer as without it, may contribute estrogens.[27]

From three to five years before a diagnosis of cancer, adenomatous hyperplasia and anaplasia are encountered with greatest frequency. No convincing studies are available to show that estrogen stimulation alone will produce this picture, and many excellent estrogen studies fail to mention such histological changes. At 49 to 52 years, women are in the menopause, which is essentially ovarian failure. Most patients destined to develop endometrial cancer have a menopause like that of other women. Study of ovaries at this age shows a striking loss of all follicular activity, and an increasing incidence of cortical stromal hyperplasia, particularly accompanying endometrial hyperplasia.[10, 23] To what are adenomatous hyperplasia and anaplasia of endometrium and ovarian cortical stromal overgrowth to be ascribed? Expressed most simply, since estrogen withdrawal in the menstrual cycle stimulates anterior-pituitary activity, the waning of excess estrogen stimulation in these women at the menopause may be expected to do likewise. Histological study of the anterior pituitary in postmenopausal women gives good evidence of a state of high activity in the formation and secretion of pituitary hormones.[21] Although we lack direct demonstration that endometrial adenomatous hyperplasia and anaplasia are due to excess pituitary stimulation in the wake of excess estrogenic effects, it seems the most likely explanation at present. The pituitary effect could be either direct or mediated by ovarian cortical stroma. What part the adrenal cortex may play is unknown.

The appearance of carcinoma in situ about three to five years before diagnosis of cancer is made seems to represent a histologically recognizable mutation in the metabolism of some endometrial glands. Pending consideration of the validity of this concept by others, it would seem undesirable to discuss its origin or significance extensively. Histochemical studies will be necessary. However, it may be suggested that the menopause, which occurs most often ten years before the diagnosis of cancer, would allow two years for development of carcinoma in situ, then its uninterrupted growth for the average six years required for transition into invasive carcinoma, followed thereafter by the average eighteen months of bleeding endured by patients before they permit a curettage and diagnosis of endometrial carcinoma. This implies that normal menstruation may, in a sense, insure against the development of endometrial carcinoma, at least when it follows an ovulatory cycle. In the small group of young women who have endometrial carcinoma before 35 years of age, there is frequently a clinical history of irregular, profuse menses and sterility. Investigation shows that many of these women ovulate irregularly or not at all, and their endometrium is irregularly and incompletely shed. The same estrogenic and pituitary stimuli appear to be concurrently involved, as in the postmenopausal group. Like regular ovulation, parturition likewise appears to defer establishment of neoplastic endometrium. Among nulliparous women with fundus carcinoma, unmarried patients are more numerous than those who are ostensibly sterile. Whether the hormonal changes with ovulation and pregnancy are more important in maintaining normal endometrial physiology or whether it is the complete endometrial shedding that occurs with menstruation or delivery, or both, is at present uncertain. The minimal postpartum interval found in our cases before carcinoma developed was four years, and in the vast majority the interval was ten to forty years (Table 3).

The most popular present theory of the etiology of endometrial carcinoma involves excess estrogen stimulation. The frequency, up to 20 per cent, with which fundus cancer accompanies estrogenic ovarian tumors such as the granulosa- and theca-cell types is usually mentioned in support. This reasoning fails to account for the origin of the ovarian neoplasms. Excellent experimental work has recently demonstrated that intrasplenic implants of ovaries develop these tumors, the liver inactivating ovarian hormones so that the transplants are continuously under pituitary stimulation.[14] The present study suggests that long-continued pituitary stimulation of

uterus and ovary, following a period of prolonged or increased estrogen effect, may often end in carcinoma of the endometrium.

No unusual incidence of myometrial leiomyomas was found, and half these accompanying tumors showed hyaline degeneration or calcification. The stimulus, estrogenic or otherwise, that evoked these now degenerated leiomyomas must have long since ceased.

Other stimuli may doubtless be involved. Radiation damage to endometrium may lead to cancer, particularly carcinosarcoma. In large series, many of the patients with malignant endometrial tumors are 60 to 75 years old. In three of the four in this age group in the biopsy series who had had previous biopsies taken postmenopausally, endometrial polyps were present and radiation had been administered Malignant change in endometrial polyps is relatively common and may be particularly important as a cause of endometrial cancer after 60 years of age.

Of biological interest is the rabbit tumor described by Greene, arising in the uterus after a long period of reproductive disturbance, passing through adenomatous stages, and ending as a very malignant, metastasizing, and transplantable carcinoma. It is sufficiently like the analogous neoplasm in women to provide good experimental material for further animal investigation.

Summary

A series of 500 cases of endometrial carcinoma has been analyzed, 389 of these in detail. It was possible to collect thirty-two cases in which previous endometrial biopsies had been taken one to twenty-three years before the diagnosis of carcinoma. Those taken fifteen or more years before the recognition of cancer were essentially negative, while most biopsies made at shorter intervals were abnormal. Endometrial polyps and cystic hyperplasia were met most frequently six to thirteen years before the diagnosis of cancer was made. Adenomatous hyperplasia and anaplasia were most common three to five years before cancer. None of these changes is considered irreversibly neoplastic. Carcinoma in situ of the endometrium was observed six times, most often three to five years before the diagnosis of invasive carcinoma. The thirty-two cases had an age range, histological appearance, and mortality comparable to the group of endometrial carcinomas as a whole. Radiation therapy had been administered to twenty patients, which may account for the three carcinosarcomas in the biopsy series.

Statistical analysis of the entire group of endometrial carcinomas indicated frequent association with obesity, diabetes mellitus, and nulliparity, suggestive of some common metabolic disorder. Evidence is presented suggesting pituitary-ovarian dysfunction in these patients. Excessive estrogen stimulation of the endometrium followed by prolonged, excessive, anterior-pituitary stimulation of the endometrium and the ovary are correlated with the successive morphological changes ending in endometrial carcinoma.

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GENESIS OF ENDOMETRIAL CARCINOMA

*II. Cases 19 to 35 Years Old**

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THE occurrence in infants, children, and adolescents of endometrial carcinomas comparable to those of adults is practically unknown. Of such alleged corpus cancers reported, some were considered by the original authors to be of endocervical origin,[2, 16, 21] others affected both ovary and uterus and probably originated in the ovary,[1, 9] and the remainder were mixtures of carcinoma and sarcoma.[1, 8] The youngest of these patients, 15 months old, had an adenosarcoma of Wilms's type.[15] Apparently the influences leading to endometrial carcinoma do not become operative until after puberty.

AGE

The youngest patient in whom an authentic endometrial carcinoma was encountered in a search of the literature was 16 years old.[13] Although unusual, several other acceptable cases have been recorded at less than 20 years,[10, 18, 21, 27] and the age incidence rises steadily thereafter. Most series of endometrial cancer include some patients less than 35 years of age. Therefore, in menorrhagia, metrorrhagia, or supposed incomplete abortion occurring at whatever age, it is important to examine the curettage material histologically, whether it was obtained for diagnostic or for therapeutic reasons. Menorrhagia has led to investigation and diagnosis of carcinoma in most young patients. In reproductive, menstrual, and hormonal respects as well as age, they differ from the relatively more frequent postmenopausal endometrial carcinomas.

CLINICAL ASPECTS

Detailed analysis of thirty cases, 16 to 35 years old, collected from the literature[1–7, 10, 11, 13, 14, 17–19, 20–30] is impossible, because there was no consistent recording of various data, aside from age and diagnosis. Thirteen of the group were stated to be married, and six were single. In all, twelve were nulliparous; two patients had borne one child each; one woman had five offspring. Cancer had been recognized from seven months to six years postpartum. Seventeen patients gave histories of menorrhagia, and one had never menstruated. Three were described as obese. Three had had radiation therapy for benign conditions from two to thirteen years before, and two of these developed carcinosarcoma. At operation, ovaries were observed to be normal in three cases, to have perioophoritis in two, and to be very large without evidence of previous ovulation in four patients. There were three deaths from cancer; other cases were reported well from ten months to eight years after operation.

NEW MATERIAL

Because of the clinical and pathological differences, and theoretical interest in young patients with endometrial carcinoma, eight cases, 19 to 35 years old, studied at the Free Hospital for Women, have been collected, together with eight examples seen in consultation (Table 1).† Among the sixteen women, twelve were married, and only one, the youngest, had borne a child. She stated that she had menstruated regularly throughout pregnancy. Most of the other married patients appear to have suffered from sterility, which

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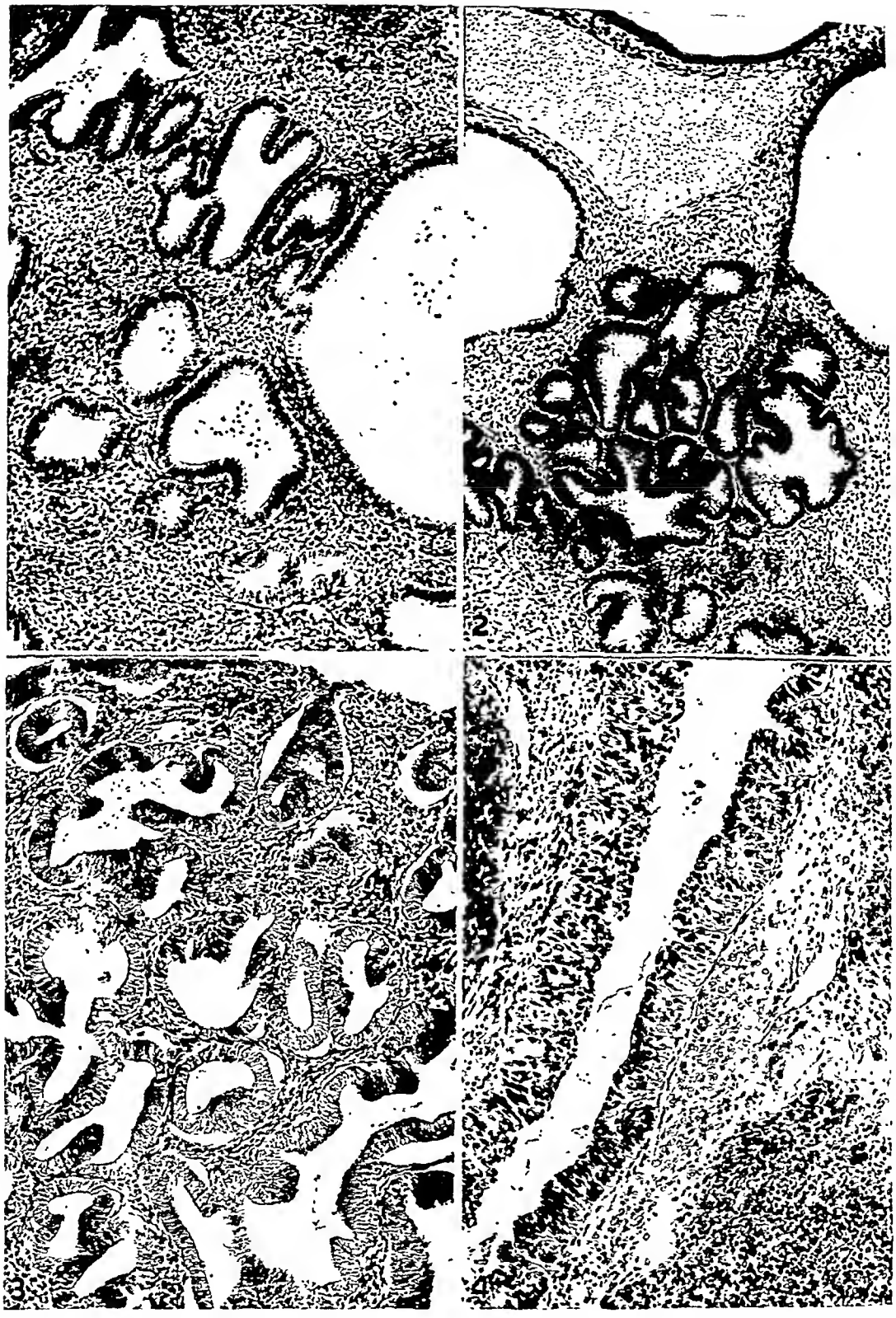

FIG. 1. *Case No. 10. Portion of endometrial curettage performed for menorrhagia. Cystic and adenomatous hyperplasia are shown. Radium, 400 mg.-hr., was administered. Patient, aged 17 years. F.H.W. 18044. (H. & E. × 100.)* FIG. 2. *Same patient, aged 22 years. Cystic and marked adenomatous hyperplasia found in endometrial polyps. F.H.W. 24843. (H. & E. × 100.)* FIG. 3. *Curettage from same case, aged 26 years. The carcinoma in situ and early invasive adenocarcinoma of endometrium illustrated were not recognized. Thyroid and progesterone were administered. B.H. S-39-1663. (E.M.B. × 100.)* FIG. 4. *Hysterectomy material, same patient as Figs. 1 to 3, age 30. Undifferentiated endometrial carcinoma, Gr. IV, metastasized, proving fatal in three months. F.H.W. S-43-794. (H. & E. × 100.)*

TABLE 1

CLINICAL AND PATHOLOGICAL FINDINGS IN 16 YOUNG PATIENTS WITH ENDOMETRIAL CARCINOMA

No	Age, yrs	Marital & fertility data	Menorrhagia duration	Maximum amenorrhea	Obesity	Radium mg hr.	Type of carcinoma	Ovaries	Outcome
1 *	19	Married; 1 child 2 yrs. o'd	2 yrs	1 mo	No, 111 lbs	No	Adeno- in polyp	Grossly neg Not removed	Well, 10 mos.
2 *	23	Single	9 yrs	9 mos	Marked	No	Undifferentiated	Fibrosis of cortex, foll cysts	Died, carcinoma, 4 mos
3.	25	Single	12 yrs	9 mos	No, 150 lbs	300, age 19	Adeno	Fibrosis, cortex, lt., cysts, rt	Well, 5 mos.
4 *	25	Single	12 yrs	Irregular	No	900 age 16	Adeno	Fibrosis, cortex, lt; endometriosis	Well, 1 yr
5 *	26	Married, no child	None	4 yrs	No	No	Adeno-	Not seen	Well, 1 yr.
6	26	Married, 5 mos., no child	12 yrs	None	No	400, age 17, 500, age 20	Adenosquamous	Focal fibrosis cortices persistent c luteu and theca-lutein cysts	Well, 8 yrs
7 *	28	Married, 5 yrs no child	16 yrs	None	?	No	Adenosquamous	Not seen	Well, 1 yr.
8 *	29	Married, 6 yrs., no child	5 yrs	None	Yes	No	Adeno	Not seen	Unknown
9 *	30	Married, 12 yrs., no child	6 wks	5 yrs	Marked, 198 lbs	No	Adeno	Mier normal	Well, 21 mos
10	30	Married, 5 yrs no child	19 yrs	5 mos	No, 143 lbs	400 age 17	Undifferentiated	Cort stromal hyperplasia	Died, carcinoma 3 mos
11	32	Single	None	None	? Yes, diabetic	No	Adeno-	Perioophoritis, cort str hyperplasia	Well, 17 yrs.
12	32	Married, 4 yrs., no child	6 mos	None	Yes, 168 lbs	No	Adeno-	Cort str hyperplasia	Well, 12 yrs.
13	32	Married, 3 mos., no child	17 yrs.	None	Marked, 198 lbs	No	Early adeno-	Fibrosis cortex, theca int hyperplasia	Well, 3 yrs
14 *	33	Married, 12 yrs., no child	3 yrs	None	Yes	No	Adeno-	Fibrosis cortex, foll cysts	Well, 1 yr
15	35	Married, 9 yrs., no child	24 yrs	9 mos	Marked, 208 lbs	No	Adenosquamous	Fibrosis cortex foll cysts	Well, 9 yrs
16	35	Married, no child	14 yrs	None	Marked, 250 lbs	1800 for ca	Adeno-	Not seen	? Recurrence 10 yrs

*Consultation case

was the presenting complaint of three. All except two had menorrhagia, and eight also had periods of amenorrhea.

Eight were obese, five to a marked degree. In several records of physical examinations the term "endocrine type" was employed, in reference to short stature and heavy build. One exhibited hirsutism. One developed diabetes mellitus ten years after cancer was found.

Eight women had had irregular profuse menses from the menarche, at times with clots and dysmenorrhea. As will be seen, this in part reflected absent or irregular ovulation and abnormal hormonal balance. Irregular endometrial shedding may be assumed as a natural accompaniment of this dysfunctional bleeding. Four patients were given small amounts of radium therapy for menorrhagia (Table 1).

PATHOLOGICAL FINDINGS

Earlier endometrial biopsies made in five of the sixteen patients showed adolescent cystic hyperplasia (Fig. 1) and endometrial polyp formation. This was succeeded later by adenomatous hyperplasia and anaplasia (Figs. 2, 5, 6), as described in our previous communication. Carcinoma in situ was observed in four cases preceding or accompanying invasive carcinoma (Fig. 3). Representative examples are illustrated to show that the

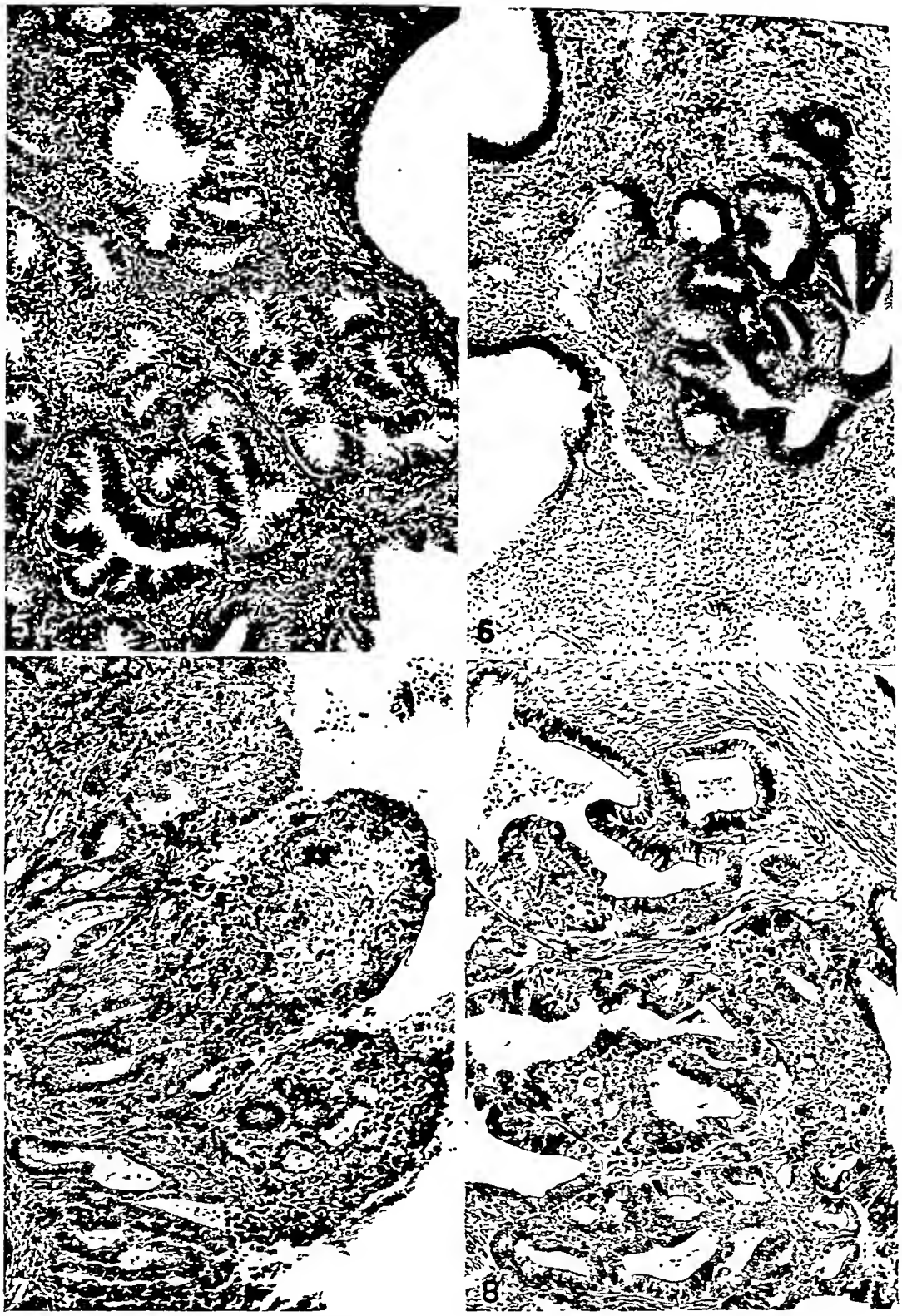

FIG. 5. *Case No. 6. Endometrial cystic and adenomatous hyperplasia with anaplasia. The patient, aged 17 years, had menorrhagia, and 400 mg.-hr. of radium was given. (This same patient had a negative secretory endometrium, not shown, two years later at age 19.) S.W.C. 23367. (H. & E. × 100.)* FIG. 6. *A repeat curettage, at age 20 years, from same patient as Fig. 5, demonstrated cystic and adenomatous hyperplasia again. Radium therapy repeated, 500 mg.-hr. S.W.C. 28199. (H. & E. × 100.)* FIG. 7. *Now aged 26 years, this same patient was a sterility problem. Curettage and hysterectomy showed adenoacanthoma, Grade I, of endometrium. The marked superficial metaplasia is evident. F.H.W. S-41-654. (H. & E. × 100.)* FIG. 8. *Invasion of myometrium by endometrial adenoacanthoma, Grade I. Same case as Figs. 5 to 7. F.H.W. S-41-654. (H. & E. × 100.)*

histogenesis of this neoplasm is the same in young as well as older patients.

At curettage, the microscopic diagnoses were adenocarcinoma in nine, adenoacanthoma (Figs. 7, 8) in three, undifferentiated carcinoma (Fig. 4) in two, and early adenocarcinoma in one. The remaining adenocarcinoma was found unexpectedly in a hysterectomy specimen removed for multiple fibroids.

Examination of ovaries was made pathologically in eleven cases (Table 1). In three of these, there was ovarian cortical stromal hyperplasia identical with that observed by Smith,[24] and Woll and others, in a high proportion of persons with endometrial cancer. Primordial ova were present without follicle formation. In one case, there was additional perioophoritis with adhesions. One had histologically normal ovarian tissue. Four patients showed grossly enlarged, smooth, pale ovaries with cortical fibrosis and subcortical follicular cysts (Figs. 9, 10). This finding is part of the Stein-Leventhal syndrome[26] of sterility, irregular menses, hirsutism, and occasionally obesity, found in young women. Two other patients had ovarian cortical fibrosis without cysts, but with markedly active luteinized stroma, and one had cortical fibrosis with endometriosis. Similar ovarian changes have been noted in a few other young women with endometrial carcinoma.[18, 25] Except in the one instance of perioophoritis, cortical stromal hyperplasia and fibrosis were not associated with inflammation and underlay normal ovarian germinal epithelium.

Therapy

Hysterectomy was performed in twelve cases, eleven of which had additional bilateral salpingo-oophorectomy. One case was considered too obese for operation, and 1800 mg.-hrs. of radium was administered. One case was untraceable after diagnosis of carcinoma. In the remaining two cases, the gynecologist did not accept the pathological diagnosis of carcinoma; each of these has been asymptomatic for one year.

Two patients are known to have died of cancer, a third is believed to have a recurrence, one is untraceable, and twelve remain alive. Eight at present have been followed less than five years since the diagnosis of carcinoma, and the other four are well after eight to seventeen years. The uncorrected five-year mortality is three of nine (33 per cent), and in cases collected from the literature, three of eight (38 per cent). With further follow-up, the mortality is expected to be considerably lower, owing to a natural selection of early diagnoses and early carcinomas.

Discussion

If one accepts these cases as carcinoma, using the ordinary morphological criteria of cytological anaplasia and histological invasion, certain factors in their genesis are apparent. Prodromal menorrhagia, lasting up to twenty-four years, at times with periods of amenorrhea, indicates frequent failure to establish normal ovulatory cycles. Biopsies of endometrium have rarely indicated progestational changes in these women. Also, microscopic examination of the large smooth ovaries commonly fails to demonstrate any corpora lutea, albicantia, or atretica. The long period of anovulatory cycles and irregular bleeding apparently allows uninterrupted local endometrial growth. Sterility is an expected concomitant.

Hyperplasia or fibrosis of ovarian cortical stroma may be sufficient mechanically to prevent rupture of ripening follicles. These two stromal conditions are not sharply distinguishable histologically and may represent different stages of the same process, as others have claimed concerning ovarian thecomas and fibromas. Beneath the overgrown stroma, the ova may lie dormant, follicles of normal appearance may form, or multiple cysts may develop. The theca interna shows variable luteinization. Taken together, these phenomena suggest effects of abnormal endocrine stimuli, rather than primary ovarian inflammatory or dystrophic disease. Experimental injections of sheep pituitary (Gonadophysin) into rabbits or women produce multiple unruptured cystic follicles like those in Stein-Leventhal syndrome. Experimental

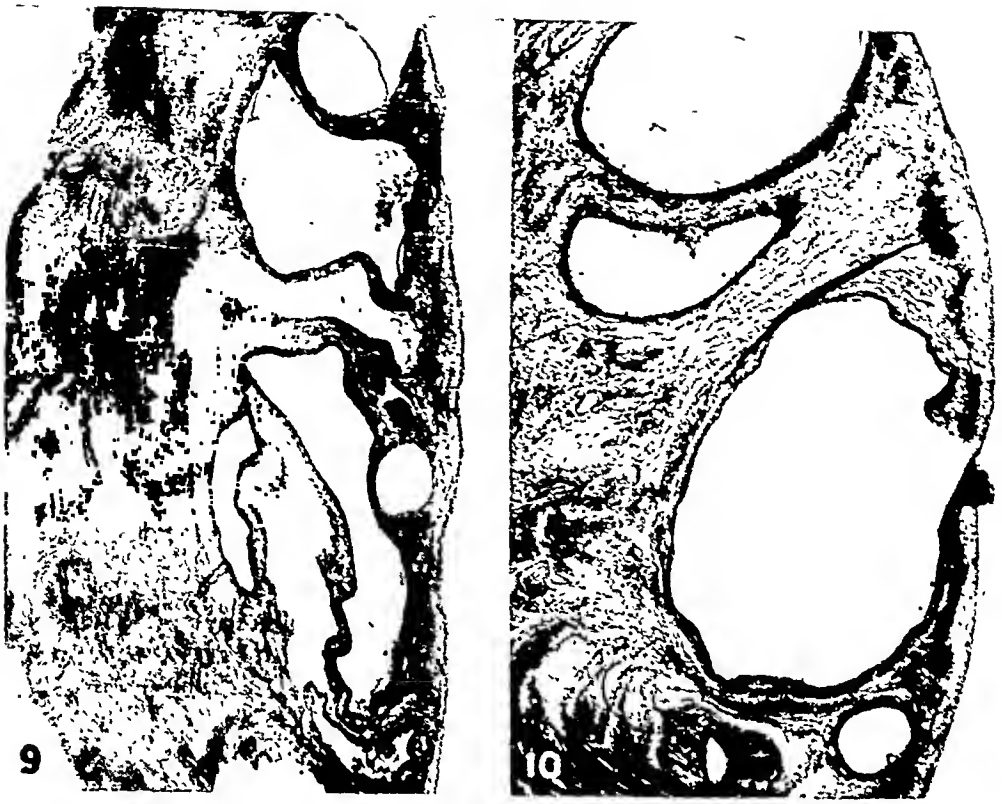

FIG. 9. *Case No. 14. Portion of ovary of woman married 12 years without a pregnancy. Obesity and hirsutism were present. Thickened ovarian cortex with subjacent multiple follicular cysts is shown, as found in Stein-Leventhal syndrome. Endometrial adenocarcinoma was present at age 33 years. D.H. 104726. (E.M.B. × 10.)*

FIG. 10. *Case No. 15. Ovary of a woman, aged 35 years, with endometrial adenoacanthoma. Fibrosis of ovarian cortex and follicular cysts are seen. Patient weighed 208 pounds, had irregular profuse catamenia since the age of 11 years, and had been married nine years without becoming pregnant. F.H.W. S-39-348. (H. & E. × 10.)*

Cushing's disease in dogs is accompanied by ovarian cortical stromal hyperplasia and dormant ova,[11] and in women with Cushing's syndrome, the ovaries appear atrophic or show cortical stromal overgrowth in youth.[4, 6, 11]

Other stigmata of endocrine imbalance already mentioned in these young women are obesity, short stature, and occasional hirsutism or diabetes mellitus. Patients with Stein-Leventhal syndrome or endometrial carcinoma in youth frequently resemble incomplete forms of Cushing's syndrome. The ovary responds to the abnormal pituitary or adrenal cortical activity in Cushing's syndrome by overgrowth of cortical stroma and inhibition of ovulation. Unfortunately, in Cushing's syndrome, endometrial morphology has been neglected, but other data indicate that pituitary, adrenal cortical, and ovarian hormones all affect its growth. This indirect information points to the importance of pituitary or adrenal cortex as well as ovary in the hormonal dysfunctions leading to endometrial carcinoma. For more direct proof, endocrine assays in women and experimental stimulation of animals must be awaited. Extrinsic influences such as ionizing radiation or therapeutic estrogens appear to play adjuvant roles in some instances.

SUMMARY

Thirty cases of endometrial carcinoma occurring in adolescence and youth have been collected from the literature, and sixteen new cases, aged 19 to 35 years, are reported. Menorrhagia, sterility, amenorrhea, and

obesity were frequently observed in this group. Their earlier endometrial biopsies showed polyps, cystic and adenomatous hyperplasia, anaplasia, or carcinoma in situ. Four were treated with radium for dysfunctional bleeding.

Ovaries were examined pathologically in eleven of sixteen patients. Three cases showed ovarian cortical stromal hyperplasia, four had cortical fibrosis with underlying follicular cysts as seen in Stein-Leventhal syndrome, and two had cortical fibrosis with luteinization of theca-interna cells. These ovarian changes and analysis of other endocrine stigmata suggest that the anterior pituitary gland, adrenal cortex, and ovary participate in hormonal imbalances considered important in the genesis of endometrial carcinoma.

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GENESIS OF ENDOMETRIAL CARCINOMA

*III. Carcinoma in Situ**

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THE morphological beginnings of most human neoplasms are unknown. In the skin and many stratified or pseudostratified mucosas, many physicians recognize the existence of a noninvasive or in situ stage of carcinoma, and there is evidence for similar developmental processes in the breast and stomach. The present communication describes a histologically recognizable counterpart, carcinoma in situ, in the endometrium.

The fundamental observation of noninvasive endometrial cancer goes back at least fifty years, described both as the earliest change and accompaniment of adenocarcinoma by Cullen and superbly illustrated (Figs. 187 and 214). Robert Meyer and Lahm later mentioned identical findings. More recently, the borderline between hyperplasia, dedifferentiation, and cancer has been disputed in numerous contradictory articles, and the idea of noninvasive endometrial cancer has been neglected. In fact, it has been claimed that myometrial invasion is the sine qua non of this neoplasm, a modified expression of the older belief that a true carcinoma is usually fatal.

Leaving aside the various philosophical arguments concerning the recognizability of endometrial carcinoma in situ, its concept is based upon these observations: (1) endometrium with carcinoma in situ later develops invasive carcinoma, (2) carcinoma in situ is found accompanying invasive cancer, (3) in endometrial polyps the in situ pattern precedes invasion, (4) evidence at hand indicates that carcinoma in situ, unless completely removed or destroyed, persists until succeeded by endometrial carcinoma.

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MATERIAL STUDIED

Clinical Features. In the period 1934 to 1948, sixty-four cases of endometrial carcinoma in situ were observed at the Free Hospital for Women. In the same period about 275 cases of invasive adenocarcinoma were diagnosed, several of which were previously or concurrently recognized in the in situ stage. Sixty cases of endometrial anaplasia and fourteen early invasive carcinomas were found during this same period; these are separate diagnostic entities and neither carcinoma-in-situ nor early invasive carcinoma cases are included in any statistics concerning invasive endometrial carcinoma from this hospital. Among the in situ cases, the age range was 25 to 68 years, with a mean age of 49 years. Twenty-three each were in the childbearing and postmenopausal groups, and eighteen were menopausal. Practically all of the sixty-four patients suffered from irregular bleeding, which confused data concerning onset of the menopause. In the postmenopausal group, flow had ceased at from 42 to 56 years, with an average of 50 years. The eleven cases with prior biopsies, mentioned later, make the assumption of continued postmenopausal bleeding appear more likely than a delayed menopause.

Of the sixty-four patients, nine were unmarried and twelve apparently sterile, or in all 33 per cent nulliparous. Twenty-eight (54 per cent) of the fifty-two with recorded weights were obese. Seventeen had had previous gynecological operations, ten had had radiation therapy for dysfunctional bleeding, and four had been receiving estrogens.

Diagnosis. No macroscopic indications of the presence of carcinoma in situ have been found. However, in one instance showing early stromal invasion microscopically, there were grossly evident focal opacities in the endometrium up to 4 mm. in diameter. Non-

TABLE 1

EARLIER BIOPSIES IN 11 CASES OF ENDOMETRIAL CARCINOMA IN SITU

				Hyperplasia			*Carcinoma*	
Interval	*Cases biop.*	*Neg.*	*Polyp*	*Cystic*	*Adenom.*	*Anaplasia*	*In situ*	*Borderline invasion*
8-17 yrs.	4	3	0	1	0	0	0	0
3-6 yrs.	6	2	2	3	2	2	2	1
1 mo.-1 yr.	3	0	0	0	1	3	2	0
TOTALS	13*	5	2	4	3	5	4	1

* Discrepancy due to one patient with three biopsies.

invasive carcinoma may exist in hyperplastic or atrophic endometrium, or in endometrial polyps. Histologically, carcinoma in situ is characterized by few or many endometrial glands composed of large cells with abundant clear cosinophilic cytoplasm. The nuclei are pale, with fine granular chromatin, and slightly wrinkled or irregular nuclear membranes arranged in irregular palisades. Some cellular disorientation and disparity in size or stratification is common, but staining quality is generally uniform (Figs. 2, 6, 10). Carcinoma in situ is often sharply demarcated and easily distinguished from adjoining normal, senescent, or hyperplastic endometrial glands. Moderate crowding of affected glands is frequent, but they do not lie back-to-back or show any invasion or displacement of endometrial stroma. The reduplication of gland lumina within glands is seen. Mitoses are not particularly helpful in recognizing either endometrial carcinoma in situ or invasive cancer. Should any invasion of endometrial stroma or myometrium be found, even locally, the carcinoma is no longer regarded as in situ.

All eosinophilic endometrial glands are not carcinoma in situ: 1. Rather commonly, in the premenstrual phase of the monthly cycle, some glands show a like coloration. Their nuclei are located slightly above the basement membrane, and the free cell margins are vacuolated and ragged. This is termed "secretory exhaustion." Stromal predecidua, the histiocytic and lymphoid infiltrate, and other indications of imminent sloughing also serve to distinguish it. 2. In chronic endometritis, eosinophilic glands may be found. Usually they show an irregular subnuclear vacuolization and wisps of intraluminal secretion or superficial vacuoles, which carcinoma in situ lacks. Nearby are plasma cells in the stroma, and some glandular and stromal cells are usually necrotic. In the presence of these indications of inflammation, the likelihood of coexistent carcinoma is remote. On the contrary, pyometra, which produces dilated gland lumina partly filled with purulent exudate but fails to involve the stroma, is a rather frequent accompaniment of endometrial adenocarcinoma. 3. Patchy areas of squamous metaplasia in the endometrium take an eosinophil coloration. 4. Anaplastic endometrial changes in women near the menopause sometimes include eosinophilic cells. Histological differentiation is more difficult, but combinations of remnants of glandular secretory activity, increased lymphocytic and histiocytic infiltration of stroma, and foci of necrosis tend to favor dedifferentiation rather than neoplasia. Carcinoma-in-situ glands are well formed, show no secretory activity, and nuclear pyknosis or cellular necrobiosis are lacking.

Developmental Stages. In addition to the patients with earlier biopsies discussed in our foregoing paper, eleven of the sixty-four in situ cases had specimens of endometrium available for review, obtained one month to seventeen years before diagnosis of endometrial carcinoma in situ (Table 1). Considering the smaller number of cases, the morphology of these preceding biopsies is strikingly similar to that seen in the larger series of biopsies prior to invasive carcinoma.

Six of the sixty-four cases, aged 26, 26, 31, 45, 48, and 65 years, proceeded to develop

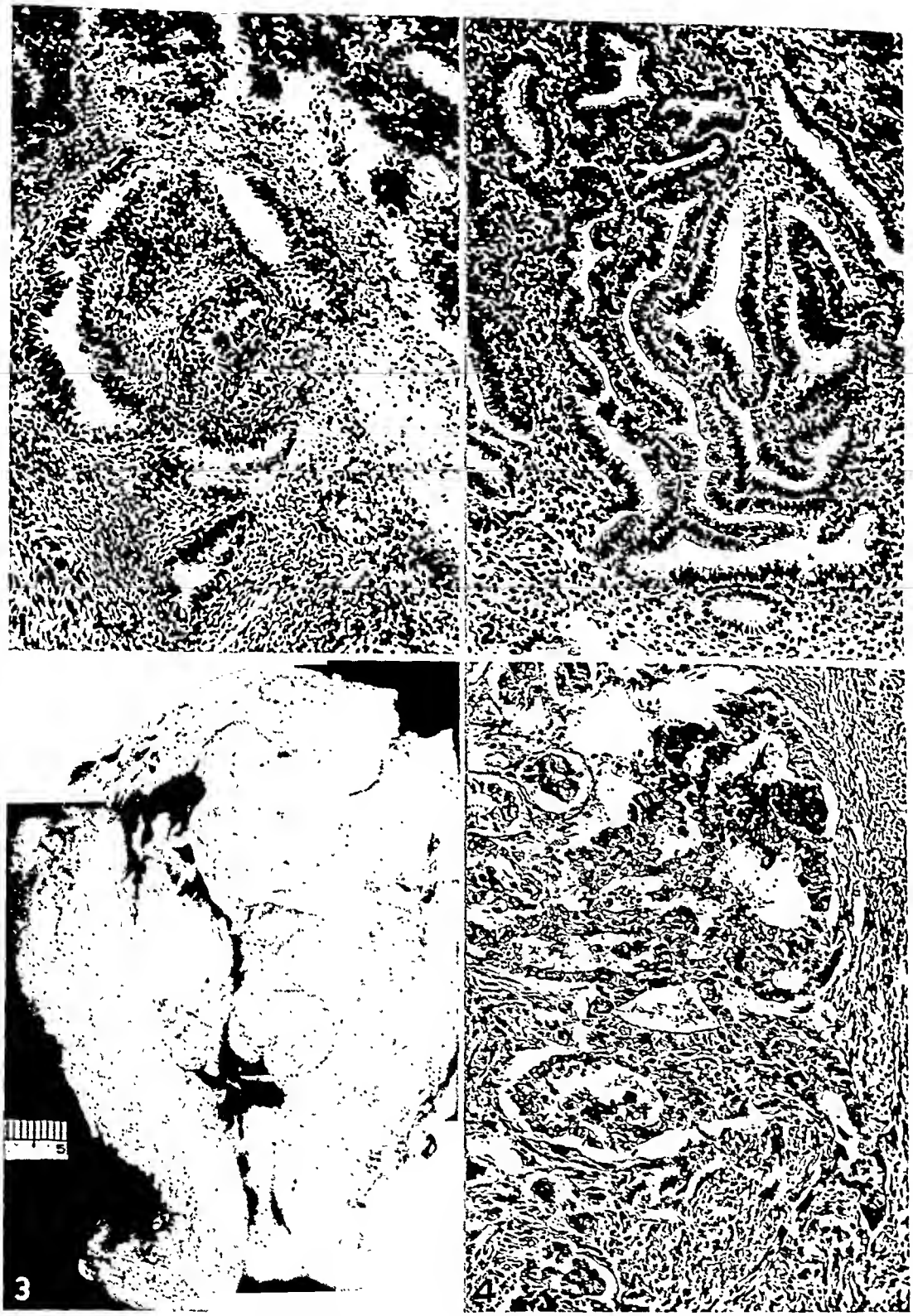

FIG. 1. *Curettage material from patient, aged 39 years. Glandular anaplasia is present in a focal area surrounded by normal menstrual endometrium. F.H.W. 24443. (H. & E. × 125.)* FIG. 2. *Typical endometrial carcinoma in situ from the same woman, aged 45 years. Pathological diagnosis was made, but clinical decision was to perform repeated biopsies; radinm, 2000 mg.-hr., was given. F.H.W. S-41-1229. (H. & E. × 125.)* FIG. 3. *Hysterectomy specimen of the same patient, four years later, aged 49 years. Typical gross endometrial cancer is present.* FIG. 4. *Microscopic preparation from the uterus of Fig. 3, with endometrial carcinosarcoma in the myometrium. The patient has remained well for four years. F.H.W. S-45-971. (H. & E. × 125.)*

invasive cancer, one to eleven years after diagnosis of carcinoma in situ (Figs. 1 to 4). Three of these patients died of cancer. They are also among the cases reported and illustrated in the preceding two communications on the genesis of this neoplasm. Five similarly acceptable cases of endometrial carcinoma in situ eventuating in invasive cancer have been reported by Gusberg (case 5), Marrubini (cases 1, 2, and 4), and Speert (case 2), so far as the descriptions and illustrations permit analysis. Terms used by these authors for the eosinophilic gland stage were adenomatous hyperplasia, doubtful malignant changes, and atypical pale glands respectively; another diagnostic phrase is atypical hyperplasia Type B (selected cases).[6]

Thus, a total of eleven patients are known who have had these sequential endometrial changes ending in typical carcinoma, and further search would doubtless uncover other instances.

Less attention has been paid to carcinoma in situ accompanying invasive endometrial cancer. Four patients in this series had both conditions side by side. They are included because the in situ portions were located basally and the invasive adenocarcinoma was in superficial or polypoid regions (Figs. 5, 6). Four other patients not included had both in situ and invasive carcinoma, with penetration of myometrium by the latter and metastasis in one instance. Cullen illustrated similar examples, as have Gusberg (Fig. 34), and Novak and Yui[7] (Fig. 12).

Development of carcinoma in situ in endometrial polyps occurred in fourteen of the sixty-four cases, not including polypoid hyperplasias. Polyps were often multiple and showed different degrees of glandular hyperplasia, anaplasia, and neoplasia (Figs. 7 to 10). Polyps occurred in equal numbers of pre- and postmenopausal patients.

Clinicopathological Correlations. The course of the six patients with carcinoma in situ followed by invasive carcinoma has been mentioned; three died of cancer, and the other three are well four or more years after hysterectomy.

Of the remaining fifty-eight cases of carcinoma in situ being reported, twenty-five were first diagnosed from hysterectomy specimens. Twenty other patients had a curettage shortly before hysterectomy. Of these twenty, two had invasive cancer in the curettings, while only carcinoma in situ remained in the endomyometrial blocks (Figs. 5, 6). Nine cases had carcinoma in situ both in biopsy and hysterectomy specimens. Five had only anaplasia in curettings, but carcinoma in situ in the sections of the uterus. The remaining four patients had carcinoma in situ by biopsy but failed to show any neoplasm at hysterectomy. Three of these had interim radium therapy of 1200 to 3000 mg.-hr. In the last patient's uterus, only basal endometrial glands remained, and all the in situ cancer had apparently been removed by the curette.

In the entire series of sixty-four cases, thirteen had curettage only and retained the uterus. Four died five months to eleven years later, ostensibly from cerebral hemorrhage or cardiovascular disease. Four have remained well after radium doses of 1400 to 3750 mg.-hr. (the patient who received 3750 mg.-hr. was also given 6000 r of roentgen-ray radiation). All these women were considered poor operative risks because of heart disease, hypertension, or obesity. The course of the remaining five cases will best serve to modify our present ideas, for they received no radiation and are being followed, with the exception of one now untraceable case. Repeated biopsies in two have shown persistence of carcinoma in situ for over one year, a not unexpected finding. The other two have shown less suspicious changes in biopsies over a six-year interval. Histologically, the characteristic eosinophilic glands in both these individuals lay in stroma showing monocytic or plasma-cell infiltration. It may eventually be necessary to discard all such findings as anaplastic accompaniments of inflammation, but in the present incomplete stage of our knowledge, this does not appear proved. One of these women, a sterility patient aged 25 years, has shown regression of morphologically typical carcinoma in situ for three years following pregnancy. These last two contro-

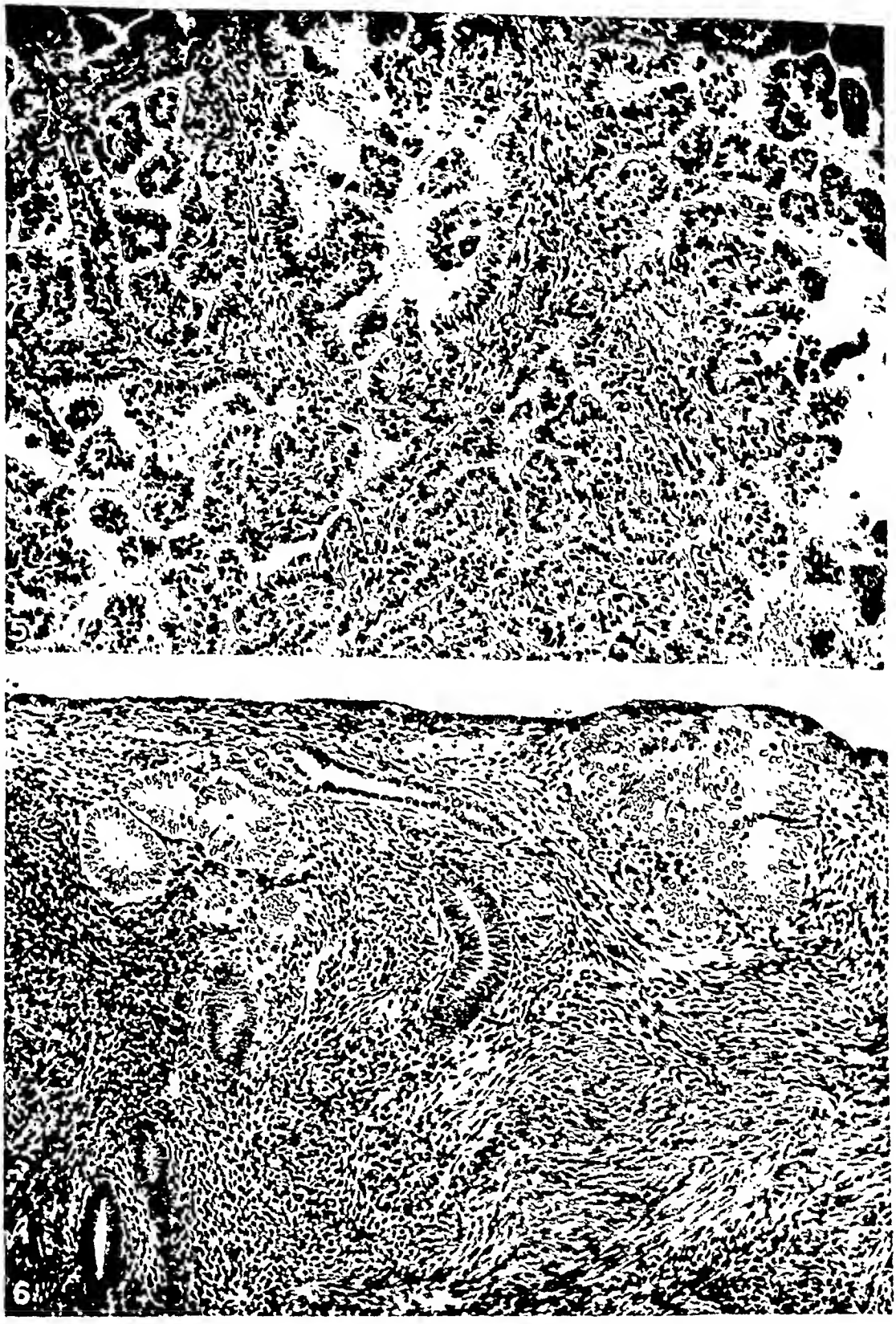

FIG. 5. *Endometrial adenocarcinoma, from curettage of a woman, aged 49 years. A negative secretory endometrial specimen had been obtained three years before. F.H.W. S-43-2200.* (*H. & E.* × *175.*)
FIG. 6. *Portion of uterine wall, from hysterectomy material, one month later. Persistent areas of endometrial carcinoma in situ are recognized by the pale eosinophilic glands. Same case as Fig. 5. F.H.W. S-43-2498.* (*H. & E.* × *175.*)

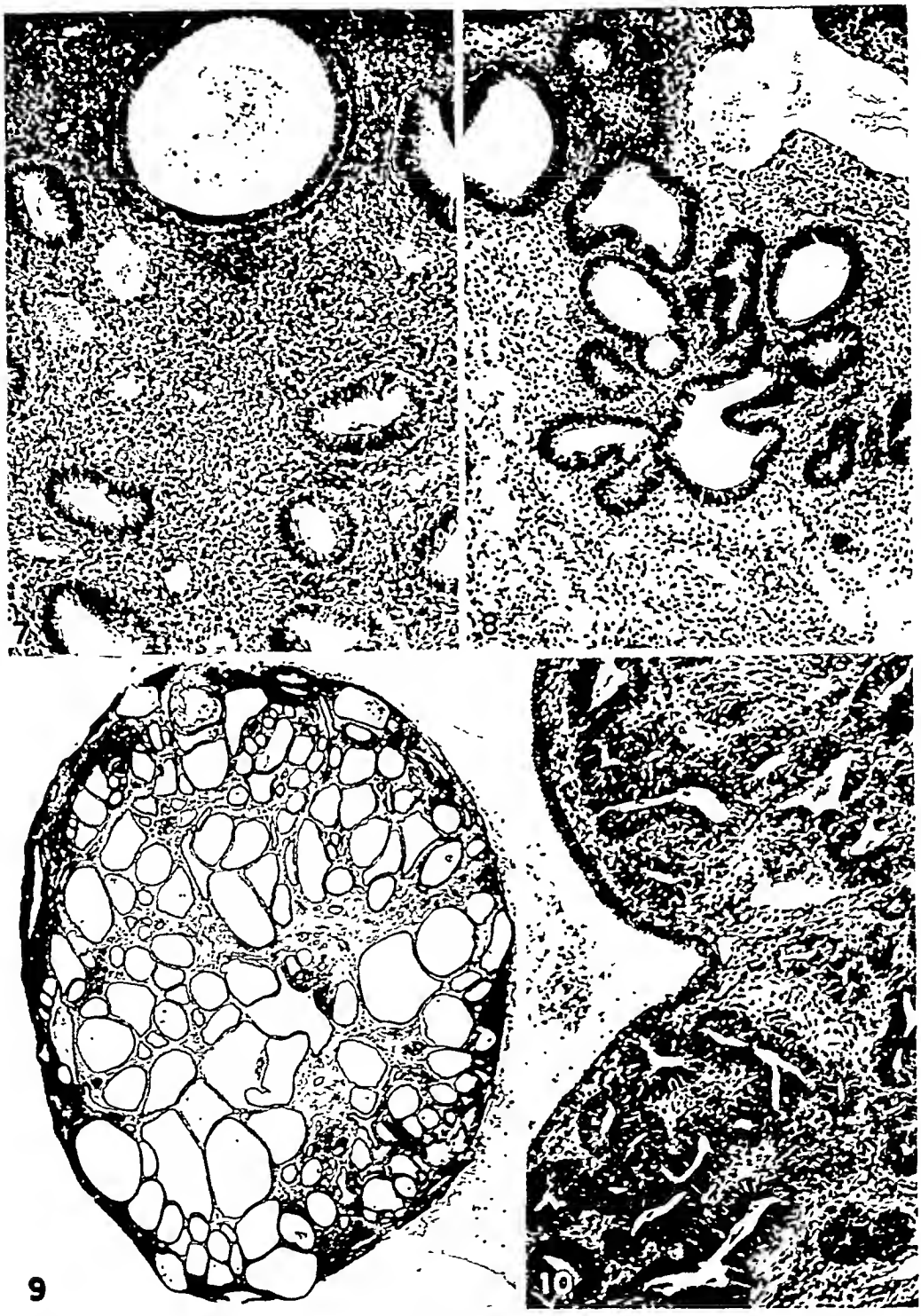

FIG. 7. *Curettage material from a girl, aged 13 years, with severe menorrhagia. Endometrial polyps were removed that contained areas of cystic hyperplasia, as shown. A small dose of radium was given. L.L. 36-1982. (H. & E. × 100.)* FIG. 8. *Repeat curettage for menorrhagia performed at age 19 years. Cystic and adenomatous endometrial hyperplasia are present. N.E.H. 1639. (H. & E. × 100.)* FIG. 9. *Same patient, at age 25 years, had a curettage showing endometrial adenocarcinoma. An accompanying endometrial polyp is illustrated. Note the small, central, cellular area. F.H.W. S-48-2032. (H. & E. × 4.)* FIG. 10. *Higher magnification of the cellular portion of the polyp shown in Fig. 9. Eosinophilic glands typical of endometrial carcinoma in situ are present. F.H.W. S-48-2032. (H. & E. × 100.)*

versial cases exemplify some problems remaining unsolved.

Ovaries. In forty cases, the ovaries were examined histologically. Outstanding abnormalities found were cortical stromal hyperplasia in seventeen, thecomatosis or cortical granulomas in seven, perioophoritis in seven, theca-lutein cysts in six, follicle cysts in six, thecomas in two, and probable granulosa-cell tumor in one.

Prognosis. No case showing only carcinoma in situ has died from noninvasive cancer, as one would expect. The invasive carcinomas that develop later appear to have the same prognosis as any group of endometrial cancers. In general, when carcinoma in situ is found after the menopause, it is considered a good indication for hysterectomy, or radiation therapy of cancer type if preferred. In younger women, careful gynecological follow-up by clinicians and pathologists with inquisitive minds may, in selected co-operative patients, help prove or disprove our contentions concerning the genesis of this tumor, without serious likelihood of harm over short periods of time.

Discussion

The developmental life history of carcinoma in situ morphologically often appears to follow a succession of endometrial polyps, cystic hyperplasia, adenomatous hyperplasia, and anaplasia. These stages may be coexistent or sequential, and may be arrested or revert to normal or senescent endometrium at any point, which suggests existence of a separate aberration of metabolism for each stage. The metabolic mutation of greatest interest is that accompanied by pale, eosinophilic, carcinoma-in-situ glands, for this seems irreversible. Perhaps histochemistry will advance understanding of the changes involved. One functioning endometrium with focal carcinoma in situ showed complete absence of intracellular or intraluminal glycogen in the affected glands, and it is hoped that further like information will be uncovered.

A typical time sequence in carcinoma in situ, based on histological and statistical evidence, would be: A patient has irregular bleeding preceding and following the menopause at 47 years of age. Biopsy shows cystic and perhaps adenomatous hyperplasia with anaplasia. At age 49 years, bleeding continues; biopsy now indicates carcinoma in situ, which has developed in the preceding two years. Carcinoma in situ is present from ages 49 to 55 years, and biopsy thereafter demonstrates invasive adenocarcinoma. In other words, with a mean age incidence of 49 years for in situ cancer and 57 years for invasive cancer, the mean duration of carcinoma in situ is eight years, less the average of eighteen months that endometrial-cancer patients wait before consulting a physician. The net duration of carcinoma in situ of endometrium is then estimated as six to seven years, comparable to about ten years for cervical carcinoma in situ. This offers hope of good clinical results accompanying early diagnoses, if conservatively made, and periodically critically re-examined.

The most important practical application of the concept of endometrial carcinoma in situ is as an aid in the early diagnosis of this neoplasm. The practicing pathologist is often confronted by the problem of whether an "atypical hyperplasia" is "precancerous," and the responsible clinical colleague requests his advice. Although the evidence presented in the present studies does not indicate that individuals inevitably proceed from cystic and adenomatous hyperplasia and anaplasia to carcinoma, the pale, eosinophilic glandular pattern of carcinoma in situ is considered irreversibly committed to neoplasia. Invasive carcinoma will succeed it if time and opportunity are allowed. It is hoped that others will attempt to prove this point to themselves, by review of older material and repeated biopsies in pertinent cases. It is emphasized that this same viewpoint has been expressed by Cullen, Robert Meyer, and Lahm, and that only the term "carcinoma in situ" is new.

Summary

A concept of the earliest, noninvasive stage of endometrial cancer, termed "carcinoma in

situ," is presented, based upon sixty-four cases. Foci of glands formed of large eosinophilic cells with pale nuclei represent endometrial carcinoma in situ, as shown by six patients who developed invasive fundus carcinomas one to eleven years after the diagnosis, eight patients with coexistent carcinoma in situ and invasion, and fourteen cases in which endometrial polyps showed the carcinoma-in-situ pattern. Similar examples are found in the literature Reasons are given for concluding that in time endometrial carcinoma in situ is succeeded by invasive carcinoma unless completely removed or destroyed.

The clinical and therapeutic aspects of endometrial carcinoma in situ are reviewed. Practically all the patients suffered from irregular bleeding. The mean age was 49 years. Eleven cases had previous biopsies that indicated a background of endometrial polyps, cystic and adenomatous hyperplasia, and anaplasia. Recognition of carcinoma in situ is believed important in the early diagnosis of cancer. It is also potentially useful in studies of metabolic aberrations that form part of the genesis of endometrial carcinoma.

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TERMINAL BRONCHIOLAR OR "ALVEOLAR CELL" CANCER OF THE LUNG

A Report of Twenty Cases

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PATIENTS with cancer of the lung are being seen at Memorial Hospital with increasing frequency. Histologically, their lesions are, for the most part, epidermoid in character, a few are adenocarcinomas of mucous-gland origin, and a small number are anaplastic epidermoid cancers of the oat-cell type. In addition, however, there is a small group of carcinomas of the lung that present a different histological picture and are associated with a specific clinical setting. In the past, these have been classified in the literature under a variety of names; i.e., alveolar-cell carcinoma, carcinomatoides alveologenica multicentrica, malignant adenomatosis, pulmonary adenomatosis, diffuse alveolar-cell carcinoma, carcinosis of the lung, and terminal bronchiolar carcinoma of the lung. It is probable that the confusion regarding a proper nomenclature for this type of carcinoma is the result of lack of knowledge of its histogenesis.

In 1876, Malassez was first to describe the multiple, nodular form of alveolar-cell cancer. His case was a 47-year-old man who gave a one-month history of dyspnea on exertion. Pleural effusion developed and he died of asphyxia. At autopsy, both lungs were found to be studded with pea-sized nodules, but the bronchi themselves were free of tumor. Microscopic study of the lesion revealed the alveoli to be lined by cylindrical, cuboidal, and flat epithelium. Papillary protrusions of tumor cells were common and some exfoliated into the alveolar spaces. The peribronchial lymph nodes contained metastatic tumor. In 1903, Musser described the diffuse form of this neoplasm. This is a rarer type that may involve a single lobe or an entire lung. It may simulate lobar pneumonia in the stage of gray hepatization. Musser also described satellite nodules in the opposite lung.

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CLINICAL ASPECTS

The present report is based upon the study of twenty cases of terminal bronchiolar carcinoma found in reviewing all the cancers of the lung at Memorial Hospital. During the past twenty years, twelve hundred cases with a clinical diagnosis of lung cancer were studied, and in 77.5 per cent of these, positive histological evidence of cancer was obtained. The earliest case of terminal bronchiolar carcinoma encountered in this series appeared in 1932. Ten diagnoses of this lesion were made in the past five years, and seven in the past two years. It is believed that many earlier cases may have been classified wrongly as mesothelioma, adenocarcinoma, anaplastic carcinoma, or metastatic carcinoma, and that therefore the true incidence of the disease at this hospital cannot be determined. The only cases included in this report are those in which the entire pulmonary lesion or postmortem material was available for study.

The symptoms and clinical course of terminal bronchiolar carcinoma do not differ greatly from those recorded for the more common types of bronchogenic carcinoma. The disease varies in aggressiveness from the most malignant type, in which death has occurred in a few months, to the clinically benign cases. Two of the latter were discovered accidentally on routine radiographic study and are now alive and well five years after operation. Metastases were noted in all fifteen patients that died. Brain metastases were noted in two instances and two patients

showed radiographic evidence of bone metastases.

In 65 per cent of the cases of terminal bronchiolar carcinoma, the history on admission pointed to a primary lung disease. Six of the twenty patients complained of symptoms now recognized as suggestive or pathognomonic of cancer of the lung. The history in six other instances simulated that of an inflammatory type of pulmonary disease; three complained of symptoms that pointed to a generalized disease such as Hodgkin's. Three patients had no symptoms, the tumor being discovered on routine chest roentgenograms taken in tuberculosis-survey studies or pre-employment films. Carcinoma of the esophagus was suspected in one instance and the remaining patient had symptoms of cardiac failure.

In this series of twenty cases, the average age was 50.4 years and one fourth occurred in women. The occupations varied from business administration in eight cases to various types of manual labor, such as plumber, mechanic, and stationary engineer. The women were all housewives. No recognized carcinogenic factor was elicited in a study of the histories of these patients. In thirteen cases data were available as to the smoking habits of the patients; three did not smoke, six were moderate smokers, and four were heavy smokers. Family histories were available in sixteen cases and three of these reported cancer in other members of the family. History of an attack of disabling influenza, twenty to thirty years before the current illness, was described in two instances. Half of the patients gave histories of prior lung disorder. One patient probably had had pulmonary tuberculosis twenty-five years before the present illness, and two reported having had pleurisy. Four patients had been told they had pneumonia in the six-month period prior to coming to this hospital.

Presenting Symptom or Chief Complaint. Pain and cough were the most common symptoms. Bloody sputum was noted in five cases, but no frank hemorrhage was recorded. The average duration of symptoms before coming to Memorial Hospital was three and eight-tenths months. Although the chief complaints varied considerably they fell within recognized groups as shown in Table 1.

TABLE 1

PRESENTING SYMPTOMS

1.	Pain (chest, shoulder, etc.)	7
2.	Pain and cough	1
3.	Cough plus wheezing	3
4.	Fever, general malaise	3
5.	Dyspnea	2
6.	Dysphagia	1

In three patients the mass was discovered at routine roentgenographic examination; no symptoms had occurred.

Physical Findings. No objective evidence of tumor was found on physical examination in nine of the twenty cases. Physical signs indicated chest disease in eight instances. Two patients had palpable tumor metastases in the skin and supraclavicular lymph nodes, and one, although in terminal stages of his disease, had no physical signs of a neoplasm. Pleural effusion was recorded as present in four instances, and two patients had clinical signs of brain metastases.

Radiographic Findings. In all twenty cases, there were abnormal shadows present in roentgenograms of the lungs. The most common finding was a single peripherally located, circular area of increased density, usually 2 to 4 cm. in diameter. This nodule (as with almost any primary lung cancer that occurs away from the hilum) seemed to differ from the usual metastatic nodule, in that it appeared more irregular, larger, less homogeneous, less sharply outlined, and in many instances, less dense. Five patients showed multiple nodules, in some involving both lungs. These cases might be confused with pneumoconiosis, miliary tuberculosis, or metastatic cancer. However, fibrosis was absent, and the nodules seemed to coalesce to form infiltrative masses. It is interesting that terminal bronchiolar cancer of the lung does not produce a characteristically diagnostic roentgenogram. However, as appears later, the radiologists made a tentative diagnosis of a malignant tumor in 65 per cent of these

FIG. 1. *Case 17. Posteroanterior preoperative roentgenogram of the chest showing an infiltrative density in the right lower lobe caused by a terminal bronchiolar carcinoma.*

FIG. 2. *Case 17. Preoperative right lateral roentgenogram of the chest showing the mass to be in the posterior segment of the right lower lobe.*

FIG. 3. *Case 17. Posteroanterior roentgenogram of chest taken four months after pneumonectomy: showing diffuse nodular densities throughout the left lung. Note the absence of fibrosis and that the apex has been spared.*

FIG. 4. *Case 17. Photograph of gross specimen, right lung, showing multiple nodules in the right lower lobe. Specimen removed two weeks after roentgenogram shown in Fig. 1.*

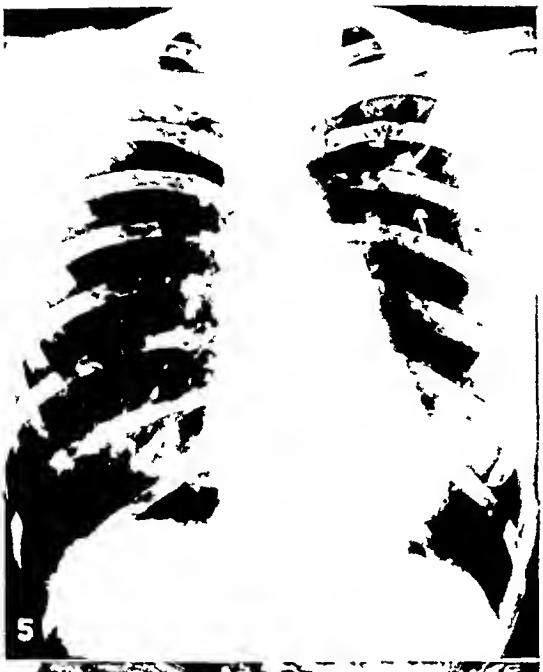

FIG 5 *Case 20 Posteroanterior roentgenogram of the chest showing circular density in left upper lobe of the lung*

FIG. 6 *Case 20 Tomograph of mass, seen in Fig 5, in the left upper lobe*

FIG 7. *Case 20 Gross specimen showing carcinoma located peripherally in the left upper lobe adjacent to terminal bronchus.*

FIG 8 *Case 10 Roentgenogram of chest showing solitary, circular, peripheral nodule in left upper lob*

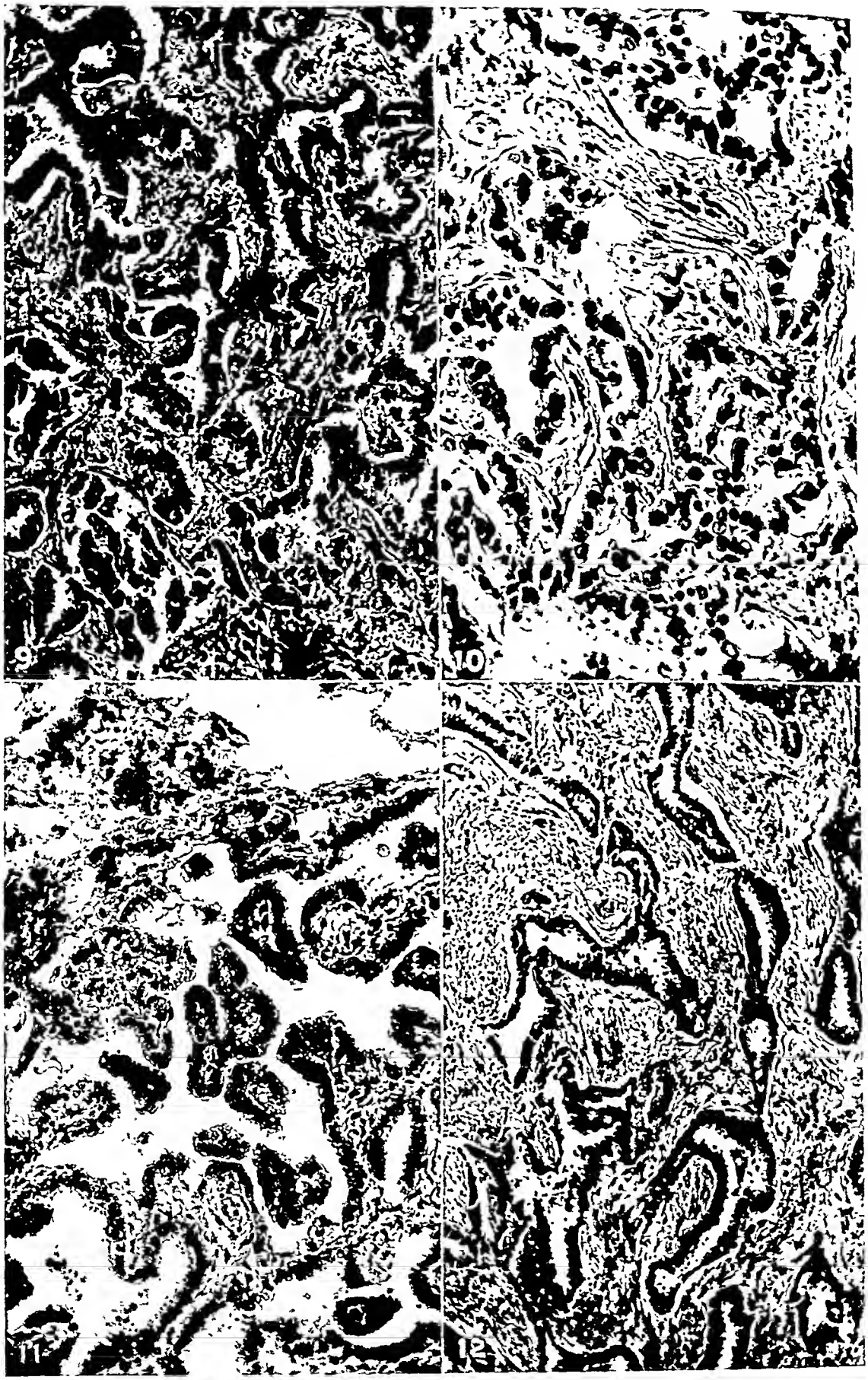

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TABLE 2

RADIOGRAPHIC INTERPRETATION

X-ray findings	*Radiographic Diagnosis*						
	Primary cancer of lung	*Lung metastases from other primary neoplasm*	*Inflammatory lesion*	*No diagnosis given*	*Neurogenic tumor*	*Hodgkin's disease*	*Total no. cases*
Solitary circumscribed mass	7	0	1	0	0	0	8
Multiple nodules	0	3	1	0	0	0	4
Infiltrative density	0	0	1	0	0	0	1
Hilar mass	1	0	0	1	0	0	2
Mediastinal mass	0	0	0	0	1	1	2
Pleural effusion only	0	0	0	2	0	0	2
Mass filling entire chest	0	0	0	1	0	0	1
TOTAL	8	3	3	4	1	1	20

cases. In 55 per cent of the series, the tumor was reported to be in the lung parenchyma and in 40 per cent of the cases a definite radiographic diagnosis of primary carcinoma of the lung was made (Table 2).

Laboratory Data. Bacteriological examination of sputum is recorded in but five cases. All were reported negative for tuberculosis. Cytological studies were done in five cases, four of which were recorded as Papanicolaou Class V (or as showing conclusive proof of cancer). The other case was recorded as Class III (or as suspicious of a malignant tumor). This was a superior pulmonary sulcus tumor without evident ulceration and seemingly arising from the very periphery of the right upper lobe and extending into the mediastinal vessels and trachea. In one case in which a penumonectomy was done, the preoperative sputum was reported as Class V. After operation, the sputum became negative, but five months later it was again Class V, and roentgenograms then revealed the presence of multiple nodules in the contralateral lung.

The cytological examinations of the sputum and bronchial washings were made by Papanicolaou. A summary of his observations is as follows: "The smear method of examination of sputum and bronchial washings has proved to be efficient in the diagnosis of terminal bronchiolar carcinoma. It has been noted that this tumor exfoliates profusely as compared with other types of bronchogenic carcinoma. In the cases studied, a large number of malignant cells were recovered, showing typical cytologic changes characteristic of cancer. One of the more specific cytologic changes noted was the presence of multinucleated cells which are

FIG. 9. *Case 19. Typical area of terminal bronchiolar carcinoma. Psammoma body present in one alveolus.* (× *100.*)

FIG. 10. *Case 19. Alveoli lined by columnar neoplastic cells with a tendency to papillary formation.* (× *260.*)

FIG. 11. *Case 20. Papillary formation in terminal bronchiolar carcinoma.* (× *100.*)

FIG. 12. *Case 20. One area of terminal bronchiolar carcinoma in which desmoplasia is a prominent feature.* (× *100.*)

For captions see opposite page.

rarely seen in other types of carcinoma of the lung. It is possible that these cells may prove to be of specific diagnostic value in terminal bronchiolar carcinoma."

The peripheral-blood picture in terminal bronchiolar cancer is not that seen in inflammatory disease of the lungs. The leukocyte count varied between 7000 and 10,000. The lowest was 3400 and the highest, 14,000. The hemoglobin was exceptionally high, averaging 13 to 15 gm.; in several instances, it was 105 per cent. The red cell count averaged four million.

In the nine cases studied bronchoscopically, the tumor was not visualized. Six of the patients were too ill to tolerate bronchoscopy (terminal cases). In one case, the history obtained on admission was that of esophageal obstruction. Esophagoscopy was done, revealing an obstruction from external pressure.

Means of Establishing the Diagnosis

The literature reveals that the diagnosis of terminal bronchiolar carcinoma is most frequently made at postmortem examination. However, in our series of twenty cases, a clinical diagnosis of terminal bronchiolar carcinoma was made in nine instances. A combination of tests was used in establishing that diagnosis; i.e., cytological studies of sputum in two cases, aspiration biopsies of lung masses in four, and thoracotomy with biopsy or aspiration biopsy in three patients.

In five instances, the clinical and laboratory data pointed to a malignant lung tumor, but the exact histological diagnosis was ascertained only at the time of necropsy. In the remaining six cases, the diagnosis of lung cancer was established only after postmortem examination.

Treatment

The treatment of terminal bronchiolar carcinoma, as with cancer of the lung in general, is excisional surgery. Radiation therapy is a valuable adjunct in palliative treatment of advanced cases. Because of the extent of the disease, symptomatic treatment alone was administered in six of the twenty cases. These seemed to run a very rapid course. Three patients required thoracentesis for relief of dyspnea. Four of the patients that died in this hospital lived only three, twelve, fourteen, and thirty-five days after admission. One received terminal care elsewhere, and one was misdiagnosed as metastatic thyroid cancer and received roentgen-ray therapy to multiple metastatic bone lesions with some worth-while palliative effect. One patient who died had clinical signs of brain metastasis. Nitrogen-mustard therapy was of no value in this case. The remaining fourteen patients received either surgical and/or radiation therapy.

Radiation Therapy. Five patients received primary radiation therapy. Three had a hilar mass, one patient had diffuse nodular disease throughout the lungs, and one had a solitary pulmonary mass and pleural effusion containing tumor cells. All five patients died in four to eight weeks after completion of therapy, and no appreciable palliative effect was noted.

In a recent case, surgery was combined with irradiation in a program under study at this institution at the present time. This patient was found, at the time of thoracotomy, to have a locally resectable primary lung tumor but unresectable mediastinal masses. A segmental resection of the primary tumor was done and 56.6 mc. of radon in gold seeds

FIG. 13. *Case 20. Terminal bronchiolar carcinoma in which desmoplasia is a prominent feature.* (× *200.*)

FIG. 14. *Case 9. Area of epidermidization within a terminal bronchiolar carcinoma.* (× *260.*)

FIG. 15. *Case 14. Giant- and spindle-cell variant of terminal bronchiolar carcinoma. The tumor giant cells are irregular in shape with large hyperchromatic nuclei.* (× *260.*)

FIG. 16. *Case 19. Solid and alveolar form of terminal bronchiolar carcinoma.* (× *200.*)

For captions see opposite page.

were placed in the mediastinal masses under direct vision. This placed the radiation directly into the cancer and diminished the undesirable radiation effects on the normal lung tissue. The gold seeds also acted as excellent markers to direct the beam of supplementary high-voltage roentgen-ray therapy. This patient has since developed brain metastasis and roentgen-ray therapy to the brain has given relief of symptoms.

In summary, it is realized that five cases constitute too small a series to determine the efficacy of radiation treatment, also that most of those so treated were inoperable by present criteria of operability and, thus, were clinically far advanced. It does seem, however, that the experience with these patients indicates that radiation therapy as a primary means of treatment has little value.

Surgical Therapy. Nine patients received definitive surgical therapy. Five of these are living, and two are alive and well more than five years following excision of a solitary nodule of terminal bronchiolar carcinoma. One was treated by lobectomy and the other by simple excision of the tumor. Five of the nine patients had a complete pneumonectomy, the first of which was done in 1942. Three of these patients died from widespread metastatic carcinoma in seven, nine, and nineteen months after their operation. In two instances metastases were demonstrated in the mediastinal lymph nodes removed at the time of operation. One of these patients developed extensive cancer metastases in the remaining lung. He received both teropterin and nitrogen-mustard therapy with no apparent effect. The remaining two patients who were treated by pneumonectomy are living and free of disease three and seventeen months after their surgery.

One patient was treated by a segmental resection of the primary tumor and interstitial radon therapy to the metastatic mediastinal nodules, as described under radiation therapy. In only one of the nine patients treated by surgery was the tumor found inoperable at the time of thoracotomy. He had direct extension of the tumor to the mediastinum.

In summary, it is again realized that nine cases constitute too small a series to determine the efficacy of any form of treatment. However, an operability rate of 88 per cent is more than double that encountered in the treatment of the usual type of bronchogenic carcinoma, and suggests that this form of cancer of the lung is more amenable to surgical excision. It is also noted that the only five-year survivors in our series were treated surgically.

Pathology

The almost constant location of terminal bronchiolar carcinoma was peripheral.

Table 3

SUMMARY OF RESULTS OF TREATMENT

Treatment	*No. alive more than 5 years*	*No. alive less than 5 years*	*No. dead*
Symptomatic	0	0	6
Radiation	0	0	5
Pneumonectomy	0	2	3
Simple excision	1	0	0
Segmental resection plus radiation	0	1	0
Lobectomy	1	0	0
Exploratory thoracotomy plus radiation	0	0	1
Total	2	3	15

In the fifteen patients that are dead, there was an average interval of 9.2 months between the onset of symptoms and death.

Fig. 17. *Case 20. Metastases of terminal bronchiolar carcinoma in a pulmonary vein and perivascular lymphatics.* (× *100.*)

Fig. 18. *Case 17. Pulmonary lesion showing characteristic signet-ring cell.* (× *200.*)

Fig. 19. *Case 20. An area in terminal bronchiolar carcinoma in which psammoma bodies are found in the lumina.* (× *200.*)

Fig. 20. *Case 19. Terminal bronchiolar carcinoma.* (× *260.*)

TABLE 4. SUMMARY OF DATA: 20 CASES

No.	*Case*	*Year*	*Age*	*Sex*	*Duration presenting symptoms*	*Mos.*	*X-ray findings, chest*	*Sputum*	*Bronchoscopy*
1	A.R.	1932	62	M	Cough, chest pain	9	Multiple nodules	N	N
2	S.S.	1935	35	M	Chest pain	2	Mass filling chest	N	N
3	F.Y.	1939	42	M	Dyspnea and dysphagia	4	Multiple nodules	N	N
4	C.M.	1940	61	F	Cough	2	Solitary nodule	Tb.N.	Neg.
5	C.R.	1940	55	M	Pain, loin	2	Hilar mass	N	Neg.
6	J.H.	1942	59	M	Pain, chest	1½	Hilar mass (?)	Tb.N.	N
7	J.M.	1943	59	M	Dyspnea	1	Pleural effusion	N	N
8	D.S.	1943	48	M	Back pain	6	Hilar mass	N	N
9	E.P.	1943	41	F	Pneumonia	6	Solitary mass	N	N
10	F.K.	1944	50	M	None	—	Infiltrative mass	N	N
11	E.B.	1944	51	M	Pneumonia	5	Multiple nodules	N	N
12	F.T.	1945	28	M	Shoulder pain	6	Mediastinal mass	N	N
13	J.W.	1947	57	F	Pain, cerv. spine	10	Pleural effusion	N	Neg.
14	N.A.	1947	39	M	Chest pain	4	Mediastinal mass	P-III	Neg.
15	H.H.	1947	62	M	Chest pain	1	Solitary mass	P-V	Neg.
16	E.P.	1947	58	F	Chest pain—wheezing	1	Solitary mass	P-V	Neg.
17	D.W.	1948	50	M	Virus pneumonia	3	Multiple nodules	P-V	Neg.
18	M.S.	1948	59	M	Dyspnea	12	Patchy density	P-V	N
19	M.E.	1949	59	M	None	—	Solitary mass	N	Neg.
20	M.R.	1949	43	F	None	—	Solitary mass	N	Neg.

P-I to -V = Papanicolaou Classification of Smears; Tb.N. = tbc.neg.; N = not examined.

Seventy per cent occurred in the upper lobes. Anatomically the two forms, the multiple nodular type and the diffuse type, may occur separately or may exist jointly in the same lung or in both lungs of one individual.[7] The location of the terminal bronchiolar carcinoma was tabulated from examination of surgical specimens or autopsy material (Table 5).

The nodular form, present in thirteen cases, was characterized by the presence of multiple nodules throughout one or both lungs. The nodules varied in size from a few millimeters to 8 cm. They were discrete, irregular in outline, and occasionally the larger lesions showed soft necrotic centers. On cut section, the surface was moderately firm to soft, and varied from light gray-tan to yellow-brown. Frequently the nodules appeared as slightly raised, umbilicated masses on the visceral pleural surface. In the nodular form, ten cases showed involvement of the pleura (50 per cent).

The diffuse form of terminal bronchiolar carcinoma, involving part of a lobe, or sometimes an entire lung, was the predominant type in seven, or 35 per cent, of this series. The lung was usually voluminous and had a striking resemblance to the stage of gray hepatization of pneumonia. In no instance were cavities seen either within the involved area or in the distant lung tissue. The pleural surfaces were opaque, fibrous, or nodular. The cut surface was gray-yellow, granular, and homogenous. The adjacent pulmonary parenchyma often showed atelectasis associated with edema and congestion.

Although the bronchi were not primarily involved in either the nodular or diffuse types, they were occasionally compressed, and in one instance (case 3, Table 4), the primary bronchus was invaded by the surrounding carcinoma with secondary ulceration of the mucosa. In none of the cases was it possible to locate the site of origin on gross dissection, since the overgrowth of neoplastic tissue had obscured or destroyed any evidence from which the proof of origin could be sustained. Five instances of bilateral pleural effusion were found, there being no relation between

OF TERMINAL BRONCHIOLAR CARCINOMA

Diagnosis established by	*Location*	*Metas.*	*Treatment*	*Results from onset symptoms*
Autopsy	Multiple nodules Left lower lobe	yes	X-ray therapy	Died, 11 mos.
Autopsy	Scattered foci Entire left lung	yes	Symptomatic	Died, 2½ mos.
Biopsy skin nodule and autopsy	Right lower lobe	yes	Symptomatic	Died, 5 mos.
Autopsy	Right middle lobe	yes	X-ray therapy	Died, 6 mos.
Autopsy	Left upper lobe	yes	X-ray therapy	Died, 7 mos.
Thoracotomy	Left lower lobe	no	Pneumonectomy	Died, 19 mos. postop.
Autopsy	Entire left lung	yes	Symptomatic	Died, 3 mos.
Autopsy	Right hilar area	yes	X-rays to bone metas.	Died, 11 mos.
Thoracotomy	Right lower lobe	no	Lobectomy	Alive and well, +5 yrs.
Thoracotomy	Left upper lobe	no	V. Excision tumor	Alive and well, +5 yrs.
Autopsy	Right and left lungs	yes	Symptomatic	Died, 6 mos.
Autopsy	Left upper lobe	yes	X-ray to metastases	Died, 16 mos.
Autopsy	Left upper lobe	yes	Symptomatic	Died, 15 mos.
Thoracotomy Autopsy	Right upper lobe	yes	Thoracotomy-inop.	Died, 6 mos.
Aspiration biopsy Thoracotomy	Right upper lobe	no	Pneumonectomy	Alive and well, 17 mos. postop.
Thoracotomy	Left upper lobe	yes	Pneumonectomy	Died, 9 mos. postop.
Thoracotomy	Right lower lobe	yes	Pneumonectomy	Died, 6 mos. postop.
Autopsy	Left lower lobe	yes	Symptomatic	Died, 12 mos.
Thoracotomy	Right lower lobe	yes	Segmental resection plus radiation	Alive, 4 mos. postop.
Thoracotomy	Left upper lobe	yes	Pneumonectomy	Alive, 4 mos. postop.

the occurrence of effusion and the anatomical type of tumor. In all instances, the fluid was described as serosanguineous.

Metastasis. In sixteen cases, metastases were evident. This figure is in agreement with the tabulated data of Neuberger, who showed metastases in seventeen of twenty-five cases. Of twenty cases tabulated by Adler, thirteen showed metastases. Approximately one third of all of their cases failed to develop metastasis; in only 20 per cent were metastases generalized. Metastatic spread is most commonly seen in the same lung or to the opposite lung and to the peribronchial or hilar lymph nodes. The site of metastasis was established by necropsy in ten of our cases (Table 6).

Microscopic Appearance. The microscopic sections presented a striking appearance quite unlike that seen in the more common forms of bronchogenic carcinoma. The alveolar spaces were lined by cuboidal or columnar nonciliated epithelium. Often the epithelial cells were several layers in thickness revealing a marked tendency toward papillary formation. Frequently the alveoli were distended and completely filled with the proliferating epithelial cells. Single cells or clusters of cells showing large multinucleated giant cells were found lying free in the alveolar spaces. The individual epithelial cells commonly showed varying degrees of pleomorphism. In most instances, the epithelium was fairly uniform in type with only occasional foci showing some degree of atypism. The nuclei, which were basally located, were vesicular, hyperchromatic, and sometimes irregular in outline. Relatively few mitoses were found; however, in three of the more

TABLE 5

LOCATION OF CARCINOMA

Site	*No.*
Left upper lobe	9
Right upper lobe	5
Left lower lobe	3
Right lower lobe	1
Right middle lobe	1
Right hilar region	1
TOTAL	20

TABLE 6

SITE OF METASTASES

No.	Case	Location of primary	Distribution of Metastases											
			Lungs	Para-bronchial nodes	Cervical nodes	Mes-enteric nodes	Adrenals	Kidney	Liver	Heart	Hilar nodes	Bones	Diaphragm	Chest wall	Brain
1	J.W.	Diffuse involvement left upper lobe	None						+		+				
2	W.T.	Entire left upper lobe	None	+				Right	+			Ribs, 2 and 8 vert., 2-L femur (up ⅓)			
3	A.R.	Left upper lobe	Lt. & rt. lung		+						+				
4	J.M.	Mediosup. left upper lobe	Left lung				Bilat.		+		+		+	+	
5	E.B.	Right lower lobe	None				Bilat.			++	+++	Dorsal spine	+		
6	C.R.	Left upper lobe	Bilateral	+		++	Bilat.	Left	+						
7	F.Y.	Right lower lobe	Parietal & visceral pleura		+		Bilat.	Bilat.			+				
8	S.S.	Multiple nodules, left lung	Left lung		+										+ +
9	N.A.	Sup. ⅓ right upper lobe	Lt. lung & pleura				Left	Left							
10	M.S.	Left lower lobe	None	+		+					+				

pleomorphic carcinomas with spindle and giant-cell variants, they were a prominent feature. The cytoplasm was acidophilic, relatively abundant, and surrounded by a prominent cell border.

Presence of Mucin and Fat. Vacuoles of varying degrees of prominence and size were found in the cytoplasm of the tumor cells. In certain instances in which the cytoplasm had a foamy appearance, the vacuoles proved to contain fat when differentially stained with Sudan III. Signet-ring cells, so characteristic of mucous adenocarcinoma of gastrointestinal origin, were found in ten cases. Sections from each case, together with positive controls, were stained with Best's mucicarmine. Seventeen, or 85 per cent, showed the presence of mucin in both intracellular and extracellular locations. The vacuoles of the signet-ring cells contained mucin and were indistinguishable microscopically from those seen elsewhere in carcinomas arising in mucus-producing glands.

Stroma. The stroma consisted of varying amounts of connective tissue that was greatly increased over the usual thin strands seen in normal pulmonary septa. Elastic fibers were inconspicuous. Relatively few blood vessels were seen in the stroma. Foci of inflammatory cells were observed in all of the cases especially within the alveolar spaces. The majority of these were lymphocytes or monocytes, the latter frequently associated with macrophages. Only rarely were collections of polymorphonuclear neutrophils seen, and these were most commonly associated with foci of necrosis. Hemosiderin was proved to be present within tumor cells and in macrophages with Pearl's stain. Anthracotic pigment was occasionally noted to have been phagocytized by the tumor cells.

Epidermoid Foci and Psammoma Bodies. One of the difficulties in arriving at a clear-cut diagnosis of terminal bronchiolar carcinoma was the presence of foci of epidermoid metaplasia. In those instances in which localized areas of metaplasia showed transition from the columnar epithelium to the epidermoid

type, the pathogenesis was evident. However, in some cases the epidermoid metaplasia overshadowed the less prominent features of the terminal bronchiolar carcinoma and only by multiple sections and careful study could the true nature of the neoplasm be proved.

Psammoma bodies were found within the alveoli, surrounded by tumor cells in nine cases (45 per cent). They were scattered and seldom were a prominent feature of the carcinoma.

Invasion of Lymphatics. Lymphatic invasion was demonstrated from microscopic sections in 75 per cent of the cases. Small nests or strands of tumor cells were conspicuous in the perivascular lymphatics of the small bronchiolar vessels. In one of the specimens (M.R.), serial blocks were cut of the neoplasm that was located at the periphery of the left upper lobe. Extension of strands and nests of cancer cells could be traced along the perivascular lymphatics to distant metastatic nodules lying immediately beneath the pleura. In several of the specimens, it was possible to reconstruct this setting with multiple blocks of the primary tumor and adjacent pulmonary parenchyma. Thus, the multiple nodules found in one or both lungs may well represent intrapulmonic metastasis via lymphatics. The second most common site of metastasis was the peribronchial and mediastinal lymph nodes. In each instance, the extrapulmonary metastasis duplicated the primary terminal bronchiolar carcinoma pattern. Occasionally, distant metastasis offered diagnostic problems, as, for example (D.S.), a papillary carcinoma in the thyroid was proved to be a metastasis from a terminal bronchiolar carcinoma by the demonstration of intracellular mucin in the neoplastic cells.

Correlation of Histology with Prognosis

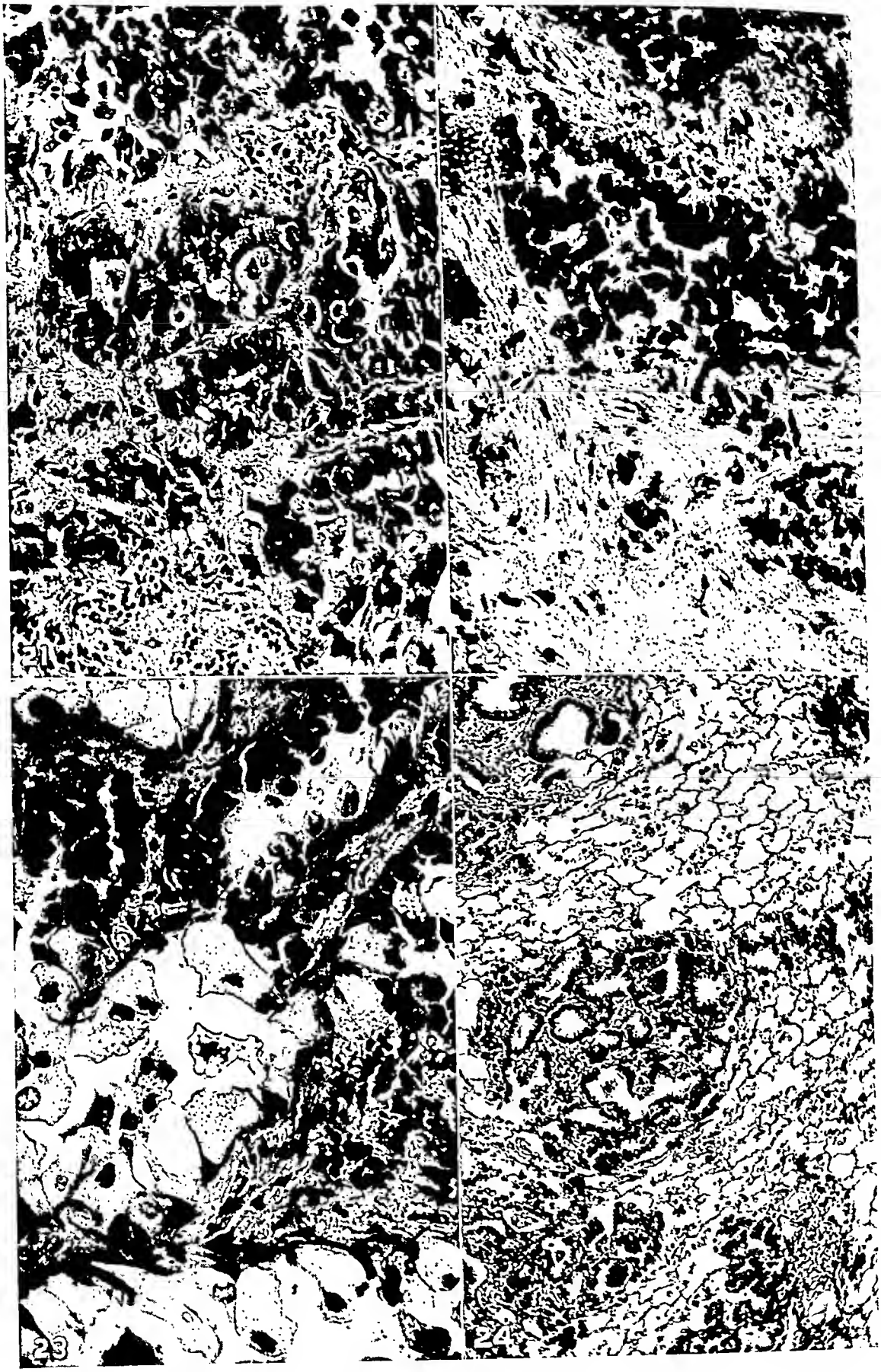
In an attempt to correlate the longevity with the histological type, it was found that certain significant criteria were evident. It is of interest that the two cases that are alive five years following surgery were both classified histologically as low-grade malignant tumors. Both cases presented a similar histological setting with a few minor variations. The carcinoma showed a uniformity of cell type with only a rare mitotic figure present. The epithelial lining was low columnar with basally placed nuclei. In some areas the epithelial cells were flattened like mesothelial cells. In one of the cases (F.K.), there was no evidence of infiltration. Psammoma bodies were noted in both cases and mucin was demonstrated in one. Giant and spindle-cell metaplasia was absent. Foci of epidermidization with marked desmoplasia were found in one case.

It was noted that those cases that had foci of the giant and spindle variant had a more rapid course than the average. The two cases in this series representing the most rapid course following onset of symptoms (two and a half and three months) showed prominent giant and spindle-cell areas with large hyperchromatic nuclei irregular in outline and numerous mitoses.

Discussion

Terminal bronchiolar carcinoma is distinguished from the more common types of bronchogenic carcinoma by distinct clinical and pathological features. Characteristically, there are two forms as described by Ewing: the multiple nodular or miliary type and the diffuse or pneumonic type. The microscopic appearance of terminal bronchiolar carcinoma, together with the failure to demonstrate origin from the primary or secondary bronchi, favors the view that this carcinoma arises from the lining cells of the terminal bronchioles and/or alveoli.

The question of the nature of the lining epithelium of the alveoli is still a controversial subject as evidenced by the discussions in recent papers.[5, 13] The current opinion appears to favor Miller's thesis of a continuous lining epithelium of the alveoli. Observations on the type of change seen in the alveolar lining in bronchiectasis and other chronic pulmonary infections support this view. Herbut,[12, 13] Ikeda, and Boone believe that terminal bronchiolar carcinoma originates from the basal cells of the bronchioles, which



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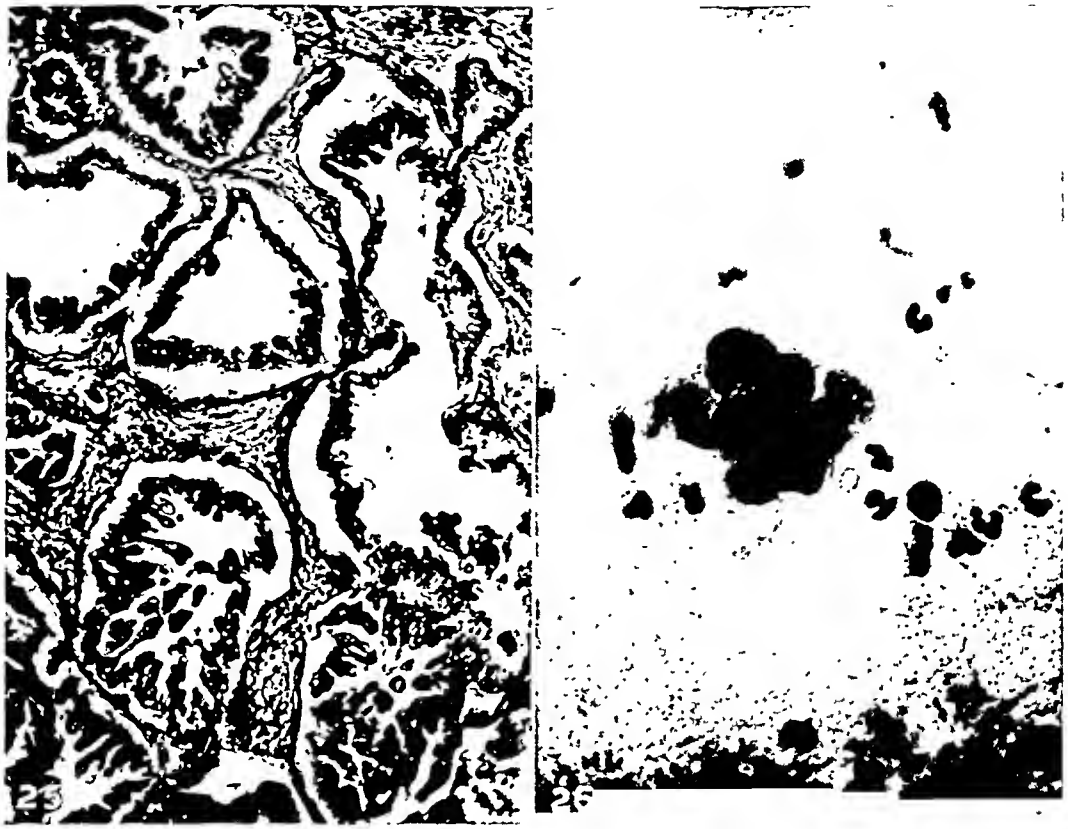

FIG. 25. "*Human jaagsiekte or so-called pulmonary adenomatosis*" (*Courtesy of the Army Institute of Pathology*).

FIG. 26. *Bronchial smear from case 17 showing multinucleated cancer cells.*

proliferate and extend peripherally along the septa. Several authors[8] contend the alveolar lining cells are mesenchymal in origin; however, sufficiently definite evidence in favor of this hypothesis appears to be lacking. From a practical standpoint, this problem is of academic interest for these neoplasms behave clinically and anatomically in a fashion similar to other carcinomas of epithelial origin.

Anatomically, there is a close resemblance between terminal bronchiolar carcinoma and pulmonary adenomatosis. The latter is characterized by tall, columnar epithelium, paucity of mitotic figures, and absence of stromal invasion. Frequently there are multicentric lesions with papillary infoldings of the lining epithelium. Several cases of so-called pulmonary adenomatosis[5, 31, 32] have been reported in which metastases occurred. Under the title of malignant adenomatosis (alveolar-cell tumors) of the lung, Dacie and Hoyle reported a case thought to be histologically and clinically benign, which was without evident metastasis at necropsy. However, on further study of multiple blocks, transforma-

FIG. 21. *Case 10. Section stained with Best's mucicarmine showing presence of intra- and extracellular mucin.* (× *200.*)

FIG. 22. *Carcinoma cells containing fat-filled vacuoles stained with Sudan III.*

FIG. 23. *Tumor cells with fat vacuoles* (*H. & E. stain*).

FIG. 24. *Jaagsiekte in lung of sheep* (*Courtesy of the Army Institute of Pathology*).

FIG. 27. *Sputum smear from case 16 showing cluster of cancer cells.*

tion to histologically malignant cells could be proved. Ewing discusses pulmonary adenomatosis as an entity; however, a search of the files in the Laboratories of Memorial Hospital failed to reveal a single case of true, obviously "benign," pulmonary adenomatosis.

Of interest in a discussion of these neoplasms of the lung is the report of the so-called occupational lung cancer occurring in miners working in the uranium mines of Schneeberg and the Jáchymov Valley of the Erz Mountains of Bohemia. Rostoski, Saupe, and Schmorl, and later Pirchan and Sikl, were able to show a very high incidence of lung cancer in these workers. The latter reported nine cases of carcinoma of the lung in thirteen autopsies done on nineteen miners who died in the year 1929 to 1930. They noted most often a circumscribed form of neoplasm. Two of the photomicrographs of their published cases suggested some similarity to the histological picture seen in cases presented in this article. For this reason, slides from four of our cases illustrating the range of histological findings in our material were sent to Dr. H. Sikl, Professor of Pathology, University of Prague.[29] He considered these tumors unlike the group of lung cancers formerly described in Jáchymov miners. A high incidence of lung cancers has also been reported among chromate workers.[16]

In laboratory animals, the carcinogenic effect of urethane, dibenzanthrene, and other carcinogens is well known. These carcinogens, whether given intraperitoneally, intratracheally, or subcutaneously, cause the development of multiple lung tumors in 100 per cent of susceptible mice within four months.[11, 22, 26, 27, 28] Many authors report the same histological picture in both the spontaneous and the induced tumors. They describe the tumor as an adenomatous tumor of alveolar-cell origin invading the lung and metastasizing to the surrounding lymph nodes. These tumors have a histology similar to that of the neoplasms described in this article.

An infectious disease of similar histological appearance occurring in sheep and other animals is known as jaagsiekte (driving sickness),[19] but is also known by various other names such as epizootic adenomatosis, infectious adenomatosis, etc.[2] It has been reported as closely resembling terminal bronchiolar carcinoma. This disease is believed to be caused by a virus that can readily be transmitted to healthy sheep by housing them with diseased animals.[6] Dungal and his associates reported one instance of successful transmission of the disease by an intrapulmonary injection of a tissue suspension. Efforts to isolate a virus or other specific agents have been unsuccessful. The histological characteristics of jaagsiekte consist of epithelial proliferations forming papillary intra-alveolar masses, which are noninvasive, singularly preserving the alveolar septa. Aynaud has reported an instance of metastases in lymph nodes and subcutaneous tissues in jaagsiekte. de Kock has suggested that jaagsiekte disease may be a true neoplasm. However, more proof is required before this hypothesis can be accepted.

SUMMARY

This report presents a clinical and histological study of twenty patients with terminal

bronchiolar carcinoma of the lung The majority of these cases ran an aggressive clinical course. Chest pain and cough were the most common presenting symptoms Fifteen per cent were asymptomatic and found on routine chest roentgenographic study. Diagnosis in most instances was made by aspiration biopsy of the mass either at the time of exploratory thoracotomy or preoperatively under fluoroscopic control, and in five instances by examination of sputum and bronchial washings.

The distinguishing feature of this disease is seen in its gross and microscopic appearance It has been divided grossly into a nodular (65 per cent of this series) and a diffuse form (35 per cent) Cytologically, the two forms are identical.

The only effective treatment is excisional surgery. Two of the nine patients in whom surgery was attempted are alive and well five years; one had a lobectomy and one a simple excision of the mass. Both were early cases in which a limited procedure was sufficient to eradicate the disease. Five patients with more extensive disease required a pneumonectomy. Three died and two are alive and well, seventeen and three months after surgery.

Another means of treatment that requires more study and trial is a combination of surgery and irradiation, in which the primary bulk of disease is excised and interstitial radon in the form of gold seeds is placed in the remaining, inoperable cancer. External irradiation can then be better directed to the well-marked residual cancer.

A discussion of the relationship between this disease entity and so-called pulmonary adenomatosis, jaagsiekte, occupational, and experimental lung cancer is given.

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HISTOLOGICAL STUDY OF FIVE MINUTE PULMONARY NEOPLASMS BELIEVED TO REPRESENT EARLY BRONCHOGENIC CARCINOMA

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WITHIN the last three decades, pathologists and clinicians alike have become increasingly cognizant of the importance of primary carcinoma of the lung. This is justifiably so when we consider that within such a relatively short period this entity has arisen from obscurity to a position high on the list of malignant tumors afflicting man. Indeed, recent statistical studies place this neoplasm second only to carcinoma of the stomach in the male. Concomitant with this deserved recognition, a voluminous literature concerning all aspects of pulmonary cancer has accumulated. Surprisingly enough, despite intensive studies, the actual histogenesis of this form of neoplasm has rarely been observed. Consequently, when possible, it appears justifiable to add to the meager knowledge regarding the origin of primary carcinoma of the lung.

The lack of information concerning this subject is not to be wondered at in view of the extent of the bronchial tree, the apparent slow development of carcinoma in the main bronchi, slight early symptoms referable to bronchial involvement, and the relatively silent character of some of the more peripherally located cancers. Such difficulties are further magnified by the statement of Ewing at the beginning of his section on histogenesis of primary carcinoma of the lung. "Comparatively few cases furnish opportunity to trace the sources of pulmonary carcinoma. The scope of structure is so wide, the conditions of origin so varied, and the secondary changes so numerous, that only very early cases are suitable for studies of histogenesis."

A survey of the literature for the past forty years reveals that very few histogenic studies have been carried out on early carcinomas of the lung. Eloesser included a photomicrograph in his article on bronchogenic carcinoma, revealing the possible source of origin of a minute adenocarcinoma from bronchiole epithelium. Stewart and Allison reported a small "oat cell" carcinoma which was accidentally found in a bronchiectatic lobe removed at surgery; however, the growth was lost in serially cut sections before a point of origin could be established. A microscopic carcinoma, with possible metastasis, originating in a ductus alveolaris has been ably described by Gray and Cordonnier. Womack and Graham have reported a similar process, which they discovered in three patients operated upon for congenital cystic disease of the lung. Although they admitted the abnormality of such cellular growth, they preferred to designate it metaplasia instead of neoplasia because they felt it could not be judged clinically malignant. Moore, in his recent textbook, presents a convincing photomicrograph of a minute squamous-cell carcinoma arising from the epithelium of a small bronchiole. Although it is possible that a few similar reports may have been missed, the fact remains that studies of this type on the histogenesis of carcinoma of the lung have appeared infrequently.

AUTHORS' SERIES

This report comprises the studies made on five minute and one clinically demonstrable lung growths, which were found during the study of microscopic sections from autopsies performed by the University of Oregon Pathology Department during the past decade. Each of these minute growths repre-

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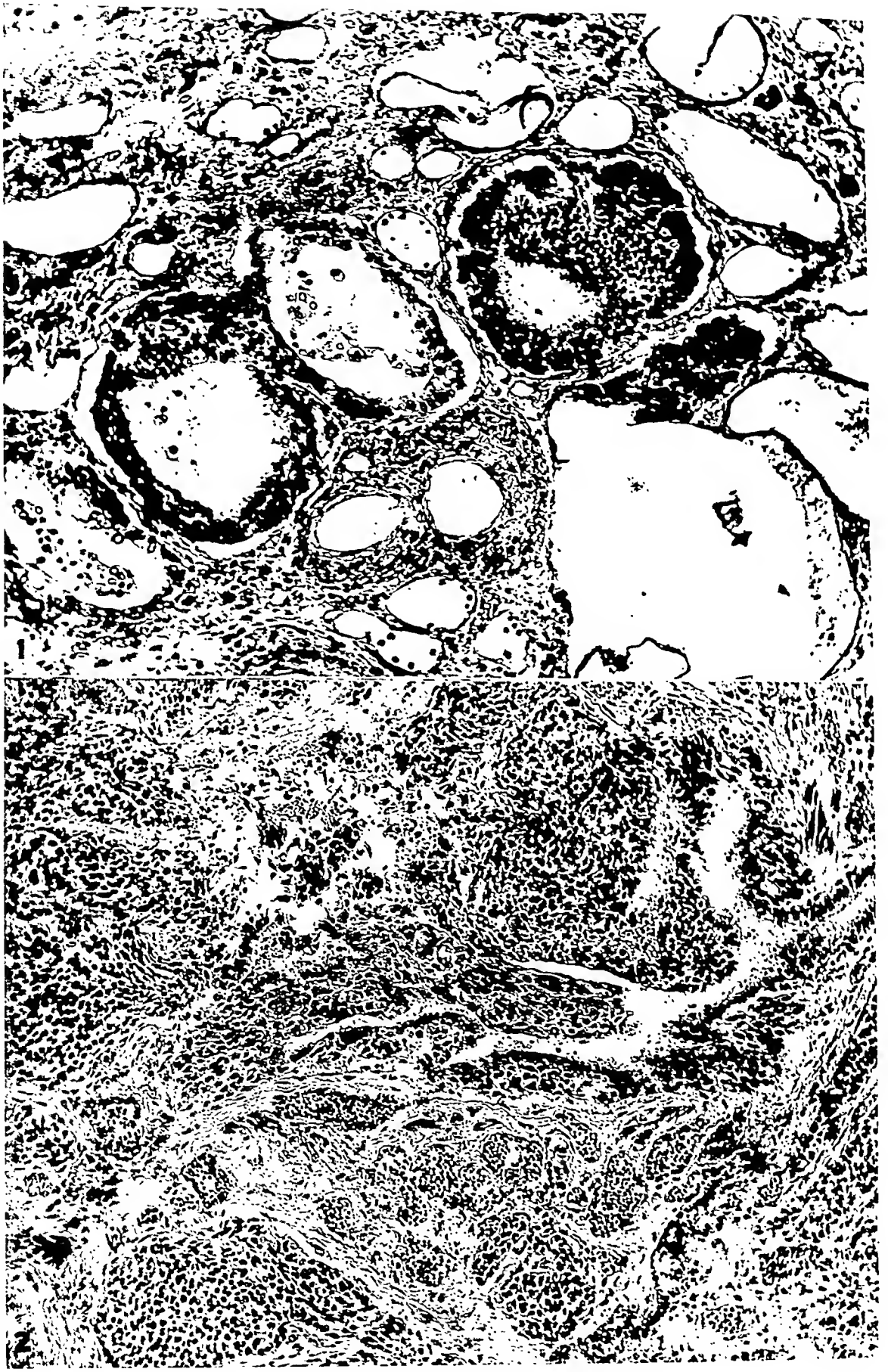

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sented an accidental finding during the examination of routine lung sections taken for microscopic study. With the one exception (M-175-5-48), none of these cases had clinical symptoms and signs during life or gross evidence at the time of autopsy that could be related to the presence of the growth. This small tumor, (M-175-5-48) measuring 2 by 3 cm., demonstrable clinically and grossly, is added for comparison.

An attempt was made in each case to obtain serial sections of the growth and in four instances this was accomplished. Unfortunately, the remaining two neoplasms could not be located on resectioning the original block. A number of attempts were made to relocate the remainder of the growths in the original lung tissue, without success.

Sections of these tumors were examined by several members of the department of pathology. It was the consensus of opinion that, because of the variability of the cell sizes and shapes, hyperchromicity of the nuclei, evidence of lymph-vessel invasion, and the presence of mitotic figures, these growths should be classified as carcinomas.

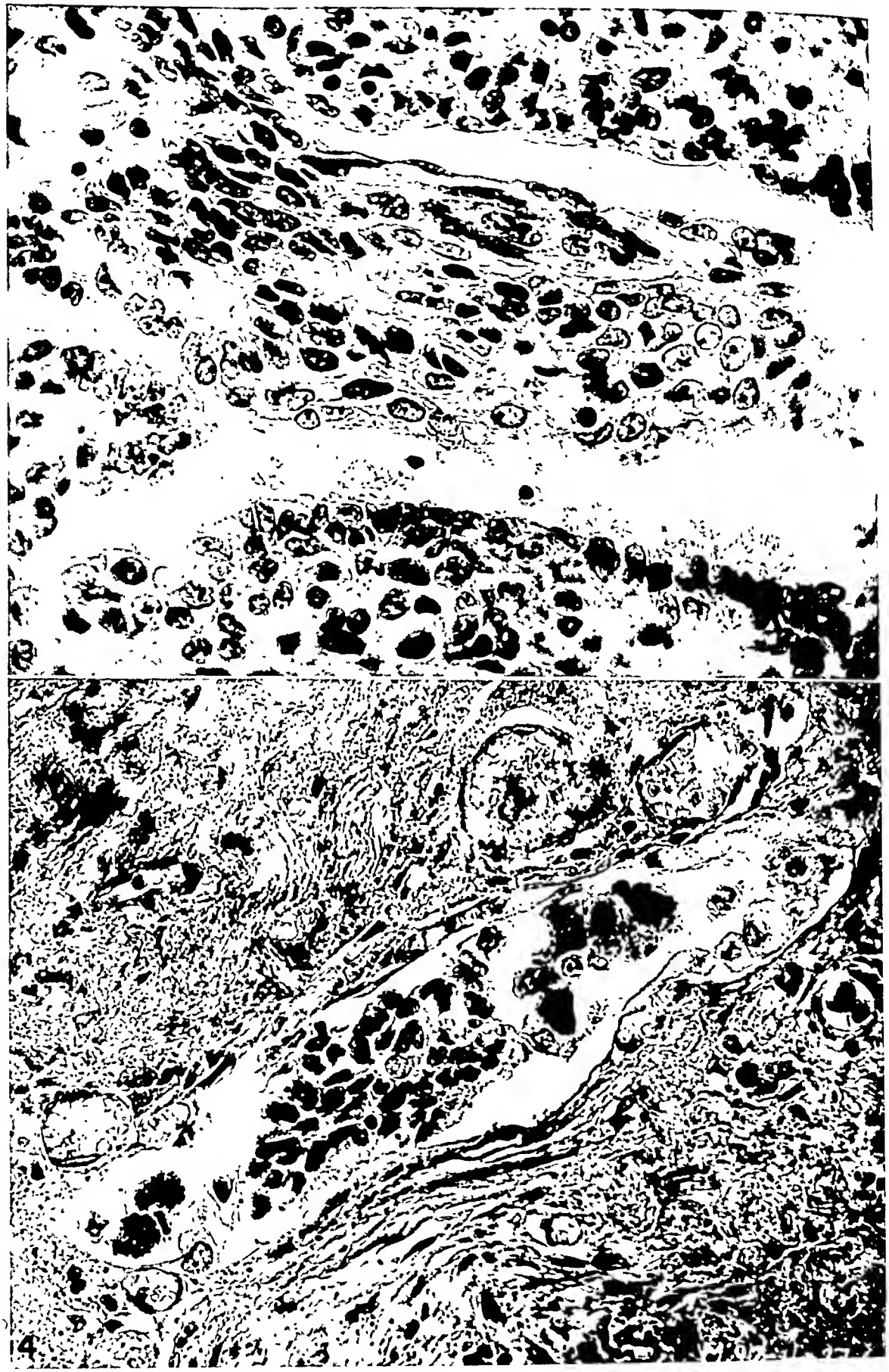
The investigation then proceeded to the careful microscopic study of some 350 serial sections cut from these tumors. Each section was examined with the primary objective of locating, if possible, areas of metaplastic epithelial change closely associated with the growth, which might substantiate an origin at that site, or foci of hyperplastic activity of the basal epithelial layer contiguous with the neoplasm. Secondarily, we attempted to study morphological characteristics and methods by which such growths extend through lung parenchyma. At the conclusion of the rather time-consuming study, we were somewhat disappointed to find that a definite histogenic site had not been located in any of the minute tumors; however, several highly suspicious areas were encountered and many other interesting findings were noted. Since neoplasms in this stage are only infrequently encountered, we feel that our findings not only may be of value in the study of histogenesis but also may shed light on some of the characteristics of these growths not discernible in the more advanced stages.

Case 1 (*Acces. No. A-89-40*). This case is that of a 69-year-old white woman, who died two weeks after undergoing a hemicolectomy for carcinoma of the cecum. Necropsy established the causes of death to be hypostatic bronchopneumonia and purulent bronchitis. It was further demonstrated that, although the carcinoma of the cecum had been completely removed at surgery, two retroperitoneal nodes contained metastatic, anaplastic carcinoma.

Existing concomitantly with the acute pulmonary inflammatory process was an area of bronchiectasis and fibrosis in the apical region of the left lung that also revealed some rather unusual cellular changes. At several points in this fibrosed portion of the lung were small rounded openings, which could represent air sacs or possibly small bronchi. A number of these structures were filled completely, or nearly so, by oat-shaped to columnar cells with very dark staining nuclei (Fig. 1). Some of the structures, which showed incomplete centrifugal filling, contained a mucin-like substance and desquamated cells within their lumen. As these were followed in serial sections, they became solidly packed with the hyperchromatic cells. In other sections, definite columnar cells with a goblet-like appearance were noted, suggesting a bronchial origin, despite the fact that a definite connection with bronchial epithelium was not demonstrated. The resemblance to undifferentiated carcinoma of the lung was striking. Mitotic figures and actual invasion were not seen. It must be admitted that the process may represent only a marked hyperplasia of bronchial epithelium. The possibility of metastatic involvement must also be considered; but against such a conclusion was the lack of lymphatic or blood vascular involve-

FIG. 1. (*A-89-40*) *Low-power view* (× *120*) *of a focus of pulmonary fibrosis in which a few spaces, thought to be bronchioles, are partially closed by an overgrowth of small columnar cells.*

FIG. 2. (*M-92-4-37*) *Photomicrograph* (× *120*) *of a bronchiole in which a tonguelike extension of neoplasm interrupts the mucosa and is in direct continuity with a neoplastic mass outside the bronchiole. Note that part of the epithelial lining is of normal type.*



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ment, a cell type unlike that of the colonic carcinoma, and limitation of the process to the one area of fibrosis present in the lungs. Except for a lesser degree of involvement, this process was quite like some of our more definite growths.

Case 2 (*Acces. No. M-92-4-37*). This 54-year-old man entered the hospital in a semi-conscious state, and examination at that time revealed marked cardiac failure secondary to hypertensive cardiovascular disease. Routine laboratory studies were negative. He shortly developed bronchopneumonia with a concomitant bilateral parotitis, and died one week after entry.

The clinical diagnosis was well substantiated by the necropsy findings, there being ample evidence of cardiac hypertrophy and failure, renal arteriolosclerosis, bronchopneumonia, subacute parotitis, and a moderate degree of coronary arteriosclerosis. In addition, sections of one kidney and lung presented entirely unexpected findings.

One of the kidney sections revealed the presence of a small tumor, measuring 0.5 cm. in diameter. This growth, situated in the renal cortex, was surrounded by a definite fibrous capsule. Histologically, it was composed of solid sheets of polyhedral cells with a markedly acidophilic cytoplasm. No mitotic figures or evidence of vascular invasion was encountered. All indications pointed to this being a benign cortical adenoma.

In one of the routine sections of the lungs, lying 5 mm. beneath the pleura, there was a small cellular area, measuring 3 by 1 mm. A short distance inward from the mass, a tangentially cut bronchus, too small to have cartilage but possessing a well-defined muscularis mucosae was found. In close proximity, a still smaller bronchus, cut transversely, lay just within the outer margin of the minute growth. The smaller bronchus also had a muscularis mucosae and in its lumen were large cells with a foamy cytoplasm, presumably monocytes.

Completely surrounding the smaller bronchus and extending the width of a number of air sacs beyond its wall were dense accumulations of cells, sometimes filling the alveoli completely, in other instances, especially at the periphery, only partially so.

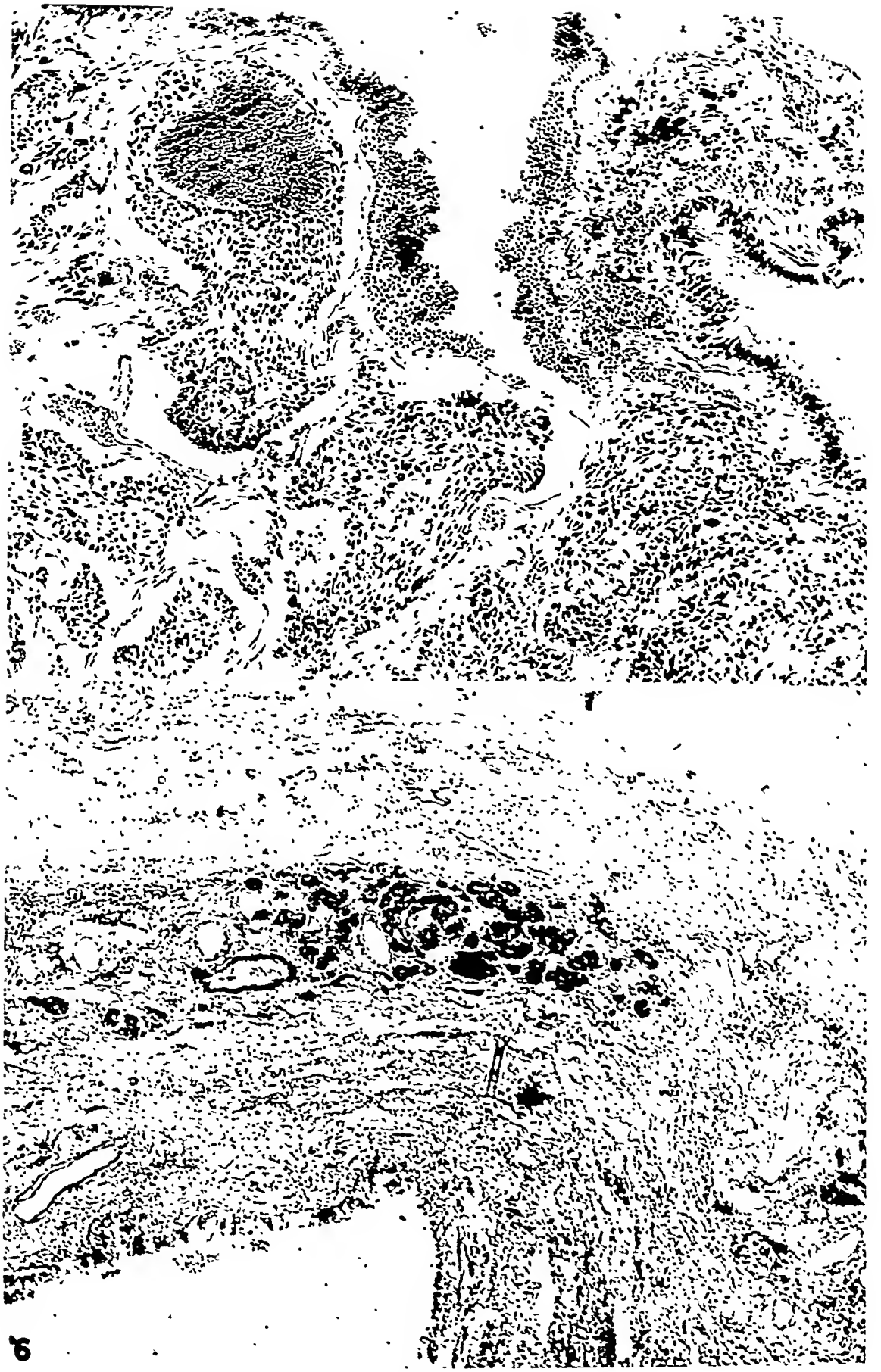
The epithelium of the bronchus presented a variable structure; parts of it consisted of a single layer of cuboidal cells; other segments displayed the normal pseudostratification of bronchial epithelium. Two additional areas were quite different. For a short distance, the single to double layer consisted of much elongated cells; at still another point, one encountered normal-appearing columnar cells along the immediate border of the lumen, underlaid by a zone of small cells like those normally found in the germinal layer. Finally, another group of elongated cells, apparently continuous with a discrete mass of epithelial cells within the bronchial wall, was noted where the germinal cells should be. Again, in the fibrous portion of the bronchial wall, with many engorged capillary vessels, were two accumulations of tumor cells lying free in spaces lined by a single layer of flattened and elongated cells. It was not possible to say whether these were lymph channels or small segments of air sacs, although their presence in dense connective tissue, which appeared to be a part of the bronchial wall, was in favor of their being lymphatics. Where the involvement was insufficient to fill alveoli, one noted extension first of only one or two layers along the alveolar borders. This process shaded off to complete filling but not to obliteration or invasion of their walls.

The form of the apparent tumor cells varied according to the plane of sectioning. Many were quite long and either thin or broad, while others were ovoid or even rounded. The cell type was believed to be columnar, and in such cells, the nuclei were centrally placed, rather than at one end as in normal epithelium of this kind. The nuclei varied slightly in size, but all had both a fine and a coarse chromatin network and a few possessed nucleoli. Mitotic figures were infrequently encountered. Mixed with the well-preserved cells were a few with small and pyknotic nuclei.

The occurrence of abnormal cells in the base of the bronchial mucosa and the apparent direct extension into the wall and the

FIG. 3. (*M-92-4-37*) *Higher magnification* (× *540*) *of the polypoid mass shown in Fig. 2. Note that the character of the epithelium changes from cuboidal or low columnar to a distinctly elongated cell. The darker nuclei are pyknotic.*

FIG. 4. (*M-92-4-37*) *A lymph vessel, surrounded by connective tissue and blood capillaries, is largely filled by neoplastic cells. The larger, dark, and granular cells are phagocytes laden with carbon pigment.* (× *540.*)



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nearby lung parenchyma, together with the probable permeation of two lymph vessels, suggested that even though minute, the growth might be carcinomatous, and it was thereupon decided to section the remainder of the block serially.

Fortunately, a large number of the serial sections were found to contain the tumor mass. These sections proceeded distally along the originally described bronchiole and a number of branches from this structure soon became intimately associated with the tumor growth. At several points, neoplastic cells were seen extending directly into the lumen of small bronchioles, and although there appeared to be a direct continuity with the lining epithelial cells, it is difficult to say whether this represented invasion or a multicentric origin. One small bronchiole, which lay in the center of the main tumor mass, presented a likely point of departure, for extending into its lumen was a tongue-like projection of the tumor (Figs. 2, 3).

The identity of this structure as a bronchiole was verified by the presence of normal surface epithelium and smooth muscle at one end; the remainder of the structure was involved by neoplastic tissue. The cells of this mass, although variable, tended to be elongated and to have a distinct chromatin network. Some of the nuclei appeared pyknotic, but mitotic figures were not seen. Under a portion of the uninvolved surface epithelium, it was also noted that the cells that were located in the area normally occupied by the basilar or germinal layer had become elongated and possessed enlarged nuclei containing a prominent chromatin network. That this change may represent neoplastic activity of the basal layer was substantiated by the gradual change from these atypical cells to the normal-appearing cells. The remainder of the tumor was well vascularized and histologically presented a picture identical with the original section previously described.

Of particular interest was one section containing a small lymph vessel in which were many cells quite like those making up the solid masses of the tumor (Fig. 4). Mixed with these were pigment-laden monocytic phagocytes. The channel in which these cells lay was lined by flattened cells and was surrounded by connective tissue containing some blood capillaries. The finding of lymphatic permeation substantiated our belief that the tumor was actually carcinomatous, even though it was minute.

Case 3 (*Acces. No. 525-11-47*). A necropsy performed on this 74-year-old white woman revealed the presence of bilateral pyonephrosis, suppurative pyelonephritis, renal lithiasis, and chronic hypertrophic ureteritis. Concomitant with the genitourinary lesions, she was found to have an acute bronchitis and bilateral pulmonary atelectasis. These findings were confirmed by microscopy, and in addition, one section of lung was found to contain a minute neoplasm that had been unsuspected on gross examination.

This neoplasm measured 2 mm. in diameter and was closely associated with a moderate-sized bronchiole, which contained cartilage in its wall. Histologically, the growth was made up of somewhat spindle-shaped cells having definitely hyperchromatic nuclei. In some, the nucleoli were easily seen, while in others this structure was not visible. Pleomorphism was prominent, but mitotic figures were infrequently encountered. The growth invaded the muscularis of the associated bronchiole at many points, and in several sections cartilage within its wall was completely surrounded. In two of the serial sections, the neoplastic cells lay just beneath the bronchiolar mucosa, but at no point could a direct contiguity be demonstrated (Fig. 5). Many of the collections of neoplastic cells within the muscularis of the bronchiole and in the lung parenchyma appeared to be in lymphatic vessels; however, no pigment-containing monocytes were noted, and the presence of an endothelial lining could not be definitely ascertained. The remaining groups of cells partially or completely filled alveoli.

On reviewing further serial sections, cut at a later date, it was readily apparent that a considerable portion of the tumor was missing. In these sections, only one small group of neoplastic cells was encountered, and these soon disappeared without again approximating a bronchiole.

Despite our inability to demonstrate a

FIG. 5. (*525-11-47*) *In this field, masses of neoplastic cells lie partly within the wall of a bronchiole* (*right*), *but more generally fill nearby air sacs. The entire neoplasm grossly measures only 2 mm.* (× *120.*)

FIG. 6. (*A-8-44*) *Photomicrograph depicting nests of neoplastic cells in the outer wall of a small bronchus.* (× *45.*)

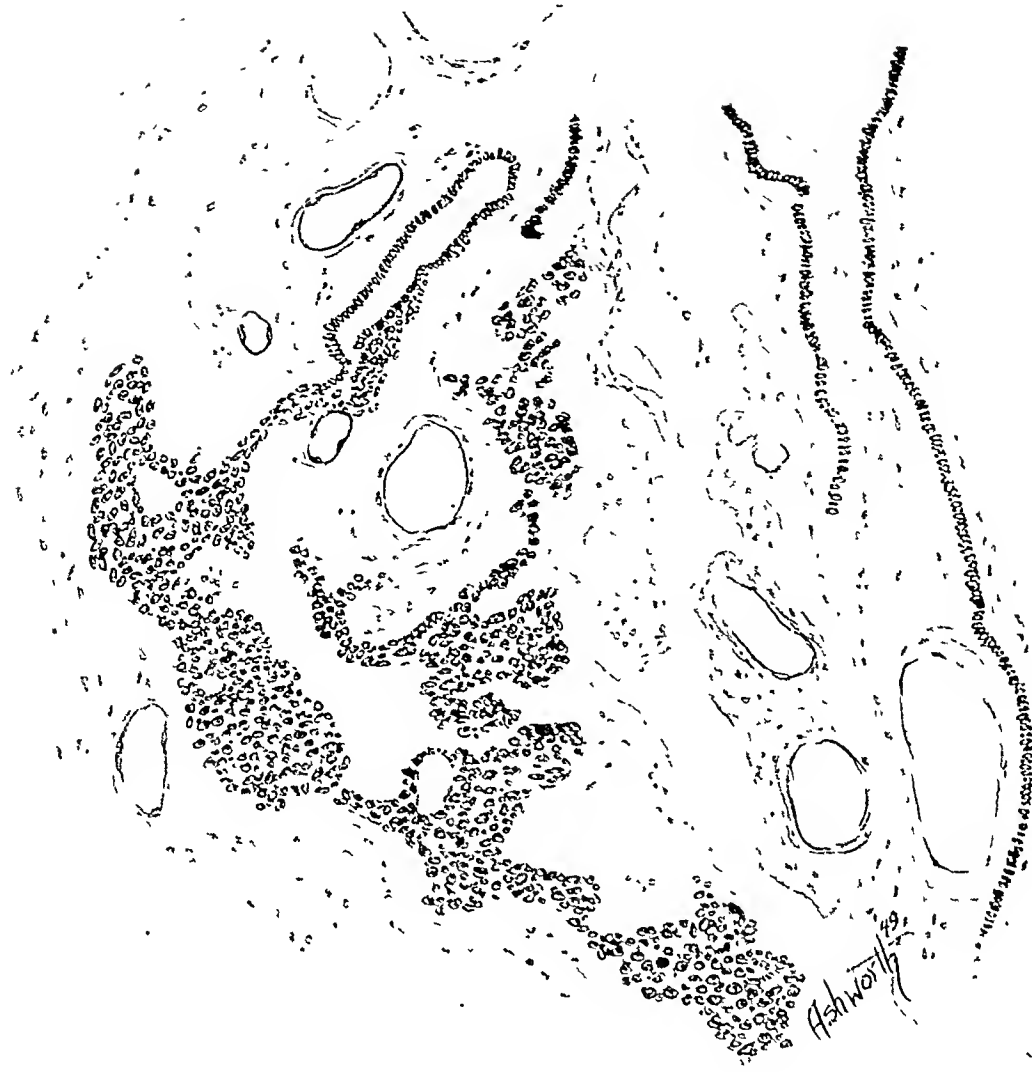

FIG. 7. *(12-1-40) Camera lucida drawing illustrating the extent and mode of distribution of the growth. To the left of center, a small bronchiole is in direct contact with the neoplasm, which has extended into a number of air sacs. The lung here is atelectatic, accounting for the collapse of bronchioles along the right border of the drawing.*

point of origin of these neoplastic cells from bronchiole epithelium, we felt that the growth represented a primary carcinoma of the lung. This contention was based on the hyperchromatism of nuclei, the undeniable evidence of invasion, and the pleomorphism of the cells that this neoplasm exhibited. In view of the absence of a cancer elsewhere in the body and because of the marked similarity of these cells to bronchiole epithelium, we believe a bronchogenic origin to be most likely.

Case 4 (*Acces. No. A-8-44*). This 52-year-old white woman died following the development of a generalized peritonitis and a mechanical obstruction of the lower ileum, which had occurred secondary to the sloughing of a rectal anastomosis. During a previous surgical procedure, an adenocarcinoma of the rectum had been excised and necropsy revealed complete removal with no evidence of extension or metastasis. In addition to focal areas of atelectasis, bronchopneumonia, bronchiectasis, and fibrous pleuritis, sections of the lungs presented microscopic collections of very deep-staining, oat-shaped epithelial cells.

Further study revealed that the collections of cells were divided into two groups by the interposition of a cartilage-containing bronchus, which was the site of bronchiectasis and chronic inflammation. The lung parenchyma

surrounding the bronchus appeared atelectatic, and it was considered most probable that these cell groups were contained in collapsed alveoli. The cell masses consisted of closely approximated, generally elongated, columnar cells with quite hyperchromatic nuclei (Fig. 6). There was no apparent invasion of blood or lymphatic vessels, and mitotic figures were not encountered.

Unfortunately, serial sections were not obtainable, so that the origin of the cells in question could not be traced. In the sections available, they did not arise from or connect with bronchioles; however, they bore a remarkable similarity to the columnar epithelium of the small bronchus within the same area. In view of the absence of mitotic figures or vascular invasion, a definite diagnosis of malignancy could not be made, and yet when one considered the growth of these cells into alveoli and the marked hyperchromatism of the nuclei, this possibility must be considered. The complete dissimilarity between these cells and the rectal adenocarcinoma precluded the possibility of a metastatic lesion.

Case 5 (*Acces. No. 12-1-40*). A necropsy performed on this 70-year-old white woman revealed the presence of bronchopneumonia involving the left upper and right lower lobes, multiple small abscesses, a purulent bronchiectasis in the lower lobe of the left lung, and a concomitant, congestive heart failure as manifested by pulmonary edema and hyperemia and pitting edema of the lower extremities. Incidental findings included degeneration of the basal ganglia that correlated well with a previous clinical diagnosis of Parkinson's disease, joint deformities secondary to atrophic arthritis, and leiomyomata of the uterus. Microscopic examination confirmed these findings, and in addition, one of the sections of lung was found to contain a small growth located just beneath the pleura.

This tumor, lying in a subpleural layer of atelectatic lung was smaller than a high-power field (10 × 43). In the original section, a small bronchiole, lined by tall columnar epithelium, was seen leading into and forming a part of the growth. At one end of this bronchiole was located an invasive type of epithelial growth with nuclei that appeared essentially similar to that of the bronchiole. These hyperchromatic cells were contiguous with the bronchiole epithelium in this section, but, since the bronchiole was not present in the subsequent sections, further confirmation was not possible (Fig. 7). The neoplastic cells were seen around blood vessels and filling what appeared to be partially collapsed alveoli; there was, however, no evidence of vascular invasion (Fig. 8). Mitotic figures were not encountered. In the serial sections that followed, the small bronchiole disappeared and the growth progressively decreased in size. While the tumor never again closely approximated the bronchiole, the cells retained their similarity to its epithelium. Consequently, even though vascular invasion and mitotic figures were not encountered, because of the marked hyperchromatism of the cells and the infiltrative tendency of the growth, we decided that a designation of beginning primary carcinoma of the lung was justifiable.

Case 6 (*Acces. No. M-175-5-48*). This 69-year-old white man died in uremic coma secondary to amyloidosis of the kidneys. Seven months prior to his death, a roentgenogram of his chest disclosed a small, discrete, 1-cm., parenchymal mass in the left upper lung field. Follow-up roentgenograms revealed the mass to be gradually progressing in size; consequently, despite several negative bronchoscopic examinations and bronchial aspirations, bronchogenic carcinoma was considered the most likely roentgenological diagnosis.

Necropsy revealed amyloidosis of both kidneys, uremic pericarditis, acute purulent bronchitis, chronic bronchitis, bronchiectasis, and a 2-by-3-cm. mass in the subpleural parenchyma of the left upper lobe. This growth did not extend through the pleura nor did it involve any of the major bronchi. Grossly, the tumor was grayish white with no evidence of hemorrhage or necrosis. Microscopically, there was disclosed an undifferentiated carcinoma with direct extension into the subpleural lymphatics, but without demonstrable metastasis. A subsequent study of serial sections failed to reveal a definite point of origin.

It is of interest that although this growth was large enough to be recognizable radiologically and was unquestionably carcinomatous histologically, it displayed certain characteristics common to all of the lesions under consideration. Except for readily demonstrable permeation of lymph vessels, this sizable tumor followed the lines of least resistance in its spread, namely, centrifugal filling of the alveoli (Fig. 9). Despite its size, there was a striking uniformity in the size, shape, and staining reaction of the individual cells.

This indicated that certain bronchogenic carcinomas may attain an appreciable size,

For captions see opposite page.

spread mainly by continuity for a time, involve only the local lymphatic vessels and display no appreciable variation in cell type. The striking similarity of this tumor and the very minute ones left us with the feeling that they were essentially alike, except for size. It might be argued that this grossly demonstrable tumor was a bronchial adenoma. Against such a contention is the histological structure and the extreme peripheral location.

At least four questions that we have asked ourselves and that may well arise in the reader's mind with respect to the growths are:

1. Do all but the one sizable tumor (M-175-5-48), included for comparison and because of identical cellular structure, represent neoplasia or merely metaplasia or protoplasia of bronchial epithelium? It is true that certain of the growths are associated with bronchiectasis, bronchitis, and focal pulmonary fibrosis—conditions in which metaplasia is a common finding. In varying degree, all displayed direct extension of growing cells into air sacs; in others, there was highly suggestive evidence of local lymphatic permeation, and in one (M-92-4-37) the bronchial wall was invaded by epithelial cells. These are the features generally accepted as bona fide evidence of neoplasia.

2. Do the cases A-89-40 and A-8-44, occurring in individuals with carcinoma of the colon with local lymph-node involvement, represent incipient pulmonary metastases? One must admit the possibility that in these two instances cells may have escaped via the vertebral system of veins and in this manner reached the lungs. Ordinarily, a hematogenous spread from rectal or cecal carcinoma would manifest itself in the liver, and this did not take place. It is true that in case A-89-40, a few of the cells were goblet-like and that mucus was present in the spaces lined by neoplastic cells, but even in this instance, the pattern was predominantly of the same cell type found in all other growths.

3. Is it possible that the small pulmonary growth of M-92-4-37 is a metastasis from an equally inconspicuous and very well-encapsulated, so-called cortical adenoma of one kidney? It is most difficult to believe that a tumor so circumscribed by dense connective tissue could be the source of the pulmonary tumor.

4. What is the possible relationship of the lesions described herein to so-called bronchial adenoma, a tumor of uncertain status but one that is today regarded by many as a form of low-grade carcinoma? It is true that all of the growths in our series present a striking uniformity of histological pattern and in this respect are like most of the bronchial adenomas one encounters. On the other hand, the cells tend to be elongated and not rounded as in bronchial adenoma, and thus bear a strong resemblance to the so-called "oat cell" type of bronchogenic carcinoma. Furthermore, the peripheral location is not in keeping with bronchial adenoma.

Discussion

Although the preponderance of evidence at the present time appears to be in favor of a bronchogenic origin for the majority of primary carcinomas of the lung, the paucity of definite histological proof still allows the question to be raised. This problem, so ably discussed by Fried, centers at the present time on three epithelial components of the lung. Ewing, in his 1940 edition of *Neoplastic Diseases*, considered that carcinoma arose from, and could be classified according to, the epithelial cells connected with three structures: (1) the epithelium lining the bronchi, (2) epithelium of the mucous glands, and (3) the epithelial lining of the alveoli. It was further his contention that the clinical history, gross anatomy, and the histological structure

FIG. 8. (*12-1-40*) *Spindle-shaped epithelial cells around blood vessels appear to be a manifestation of invasion.* (× *120.*)

FIG. 9. (*M-175-5-48*) *Photomicrograph illustrating the mode of spread of undifferentiated neoplastic cells into air sacs to the point of filling them completely.*

Dr. Robert Mehg Library

would furnish a reasonably certain and acceptable histogenic classification; however, those familiar with the variability of these neoplasms realize that such criteria will not hold. Concerning this point, Fried states: ". . . the microscopic features of a fully developed pulmonary tumor will point to its histogenesis in exceptionable cases only; the morphology of the neoplastic cells varies from one tumor to another, and even in the same tumor their form frequently varies from area to area."

In spite of Fried's admonishment, morphological and microscopic characteristics are continually used as supposedly conclusive evidence of the histogenesis of these tumors, and likewise multiple sources of origin are accepted by many. A striking example of this is the rather frequent reporting of "so-called" alveolar-cell carcinomas. This practice continues, even though there is considerable evidence that these structures may not contain an epithelial component. Miller has stated that such a layer does persist throughout life; however, in our opinion Fried's experimental results to the contrary are more convincing. Apparently in agreement with this point of view, Sweany[14] has stated that in his opinion neoplasms rarely if ever arise from the alveoli. Stout has recently reported a case in which hyperplasia and metaplasia of bronchial epithelium with extension into the alveoli closely simulated carcinomas allegedly arising from alveolar epithelium. It may well be that the majority of such growths are not primary in these structures, but represent extension or implantation from small brochogenic carcinomas that remain undetected. Likewise, metastatic carcinomas in the lungs may be a source of confusion.

The role of the mucous glands of the bronchi in the histogenesis of primary carcinoma of the lung is as yet undecided. Fried has pointed out that no one has ever observed an early neoplasm of this kind, and Letulle has excluded this variety from his classification. Much of the evidence presented in favor of such an origin has been based on the secretion of mucus or the presence of glandular structures within carcinomas of the lung; however, many investigators have pointed out that these characteristics are not infrequently seen in neoplasms arising from organs that normally secrete no mucus material. Likewise, it is not uncommon to find areas revealing these characteristics in neoplasms that are predominantly of another cell type (as in our case A-89-40). Consequently, then, although mucous glands cannot be definitely ruled out, the majority of investigators do not regard them as an important or even a likely source in the histogenesis of primary carcinoma of the lung.

By such a process of exclusion, one arrives at the remaining epithelial component of the bronchial tree—the lining epithelium, composed of a superficial and a basilar layer. The former presents a more variable histological picture with a transformation from columnar to cuboidal cells and loss of cilia as it progresses distally; however, these cells are fully differentiated and seldom digress from the normal pattern. The basal layer, on the other hand, remains quite constant throughout the entire extent of the bronchial tree. These latter cells are relatively undifferentiated, and when the bronchial mucosa is injured or destroyed, it is replaced by proliferation of the basal or germinative layer. Halpert, Sweany,[14] Fried, and many others believe this layer contains multipotential cells that are capable of giving rise to any of the epithelial components of the bronchial tree.

The actual process by which malignancy begins is as yet undecided. Many feel, however, that it is best explained by excessive regeneration of epithelium following degeneration due to some chronic irritant factor, such as long-standing inflammation. Squamous metaplasia (as encountered in tuberculous cavities, bronchiectasis, and influenza) is a striking example of this process and is considered by many to be the most common precursor of malignant tumors in the lung. Although numerous studies have appeared, no one has apparently observed the actual regeneration of columnar epithelium as evidenced by active mitosis and proliferation.

Samson, in his discussion of this phenomenon, contends that regeneration and metaplasia stem from the basilar layer and not from the adult and well-differentiated columnar cells. Similarly, Fried states: "It will be seen that the process is not a transformation of the adult columnar epithelium into a squamous type, but that a development of undifferentiated cells followed by proliferation and differentiation has occurred. The phenomenon is not a metaplasia, but a protoplasia (indirect metaplasia)."

Support for this theory has rapidly accumulated and we now find that most investigators hold the opinion, first advanced by Ribbert and Hansemann, that neoplasms usually arise from cells that are not completely differentiated. In short, this theory holds that most tissues contain both adult and embryonal or germinative cells. These germinative cells, which are usually in a basilar layer, grow out to replace adult cells that have been injured or destroyed. In most instances, this occurs without ill effects, but, should a predisposition toward cancer be present in the host, malignant cells may emerge from the basal layer and cancer results.

The acquisition of definite proof substantiating such a process has been complicated by the fact that no one has actually observed the metamorphic change of a somatic cell to a neoplastic one. As a result, our conclusions must be based on the congruous, but indirect, evidence that has been accumulated: (1) that fully differentiated cells, wherever found, are usually apotent; (2) that regeneration, which is usually the forerunner of malignancy, stems from the basilar or germinative cells; and (3) that in the bronchi, these basilar cells show every evidence of being able to form any of the epithelial components normally present.

In view of such evidence, indirect as it may be, and since we have found little to substantiate the multiple-origin theory, it is our opinion that the assignment of a bronchogenic origin to the majority of primary carcinomas of the lung is entirely justified. Likewise, as Sweany[15] has emphasized, we feel it would appear inconsistent to postulate multiple sources for the origin of pulmonary carcinoma, when there exists in the bronchi a multipotential layer capable of giving rise to any of the cells usually considered to be the precursors of the three types of neoplasms encountered: (1) undifferentiated carcinoma, (2) adenocarcinoma, and (3) squamous-cell carcinoma.

If we are ever to understand the histogenesis of the more peripheral bronchogenic carcinomas, such knowledge, of necessity, must be based upon a series of observations in minute or accidentally discovered lesions such as ours. More studies of this kind are sorely needed, and it is hoped that they will be forthcoming.

Summary

Five examples of minute and accidentally discovered pulmonary growths found in routine autopsy sections have been studied with the hope of discovering the histogenesis of primary pulmonary neoplasms. All involved quite small bronchi. In some instances, it was possible to obtain serial sections of the portion of tumor in the original block, while in others the growth quickly disappeared and could not be studied completely.

Demonstration of indubitable origin from bronchial epithelium proved to be extraordinarily difficult, but the evidence, as far as obtainable, favors bronchial epithelium rather than alveolar cells.

Two of the subjects had had carcinoma of the colon removed surgically; one of these had metastasized to regional lymph nodes. A third individual had a small and well-encapsulated renal adenoma. It is difficult for us to believe that the minute growths in the lung represent metastases from any of these, the more so because of the strikingly uniform morphology of the pulmonary growths, not only in these cases, but in two additional cases without neoplasms elsewhere than in the lung.

The presence of localized bronchiectasis and fibrosis in four of the five small tumors affords a possible clue as to altered physiology and structure which might serve as a predisposing cause for neoplasia.

Although it was not possible to establish the exact point of departure of the growths, it is of interest that although very small, all gave evidence of an ability to invade bronchial walls and to spread into nearby air alveoli. In one instance, there was satisfactory evidence of permeation of local lymphatic vessels.

The several lesions herein recorded are regarded as carcinomatous rather than mere foci of metaplasia or so-called bronchial adenomas.

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CARCINOID TUMORS—A RE-EMPHASIS OF THEIR MALIGNANT NATURE

Review of 140 Cases

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SINCE the early work of Lubarsch,[29] in 1888, a primary tumor of the gastrointestinal tract has been recognized that is present most commonly in the appendix, superficially resembles carcinoma upon histological examination, yet is distinctive in appearance and behavior. Oberndorfer, in 1907, used the term "carcinoid" for this tumor because of his belief that the neoplasm was benign, despite its resemblance to carcinoma. Masson and colleagues[19] first noted the remarkable affinity for silver salts displayed by the intracytoplasmic granules of the tumor cells and suggested that the lesion be called "argentaffin tumor." Studies of more recent years,[2, 10, 35, 45] however, have increasingly emphasized that this neoplasm is not necessarily benign, that local invasion of nodes occurs rather frequently with lesions of certain primary sites, and that distant widespread metastasis is not unknown. Our recent experience with three carcinoid tumors of the rectum[39] demonstrated the malignant potentialities of this lesion in that two patients died with extensive metastases, each within two and a half years after the onset of symptoms.

Investigation of the autopsy files from 1934 through 1948 and the surgical files from 1910 through 1948 at the Mallory Institute of Pathology revealed a total of 140 carcinoid tumors. Ninety-eight (70 per cent) of these occurred in the appendix and forty-two (30 per cent) were of nonappendiceal origin (Tables 1 and 3). None of the carcinoid tumors primary in the appendix showed evidence of regional-node involvement or distant metastasis. Sixteen (38 per cent) of the nonappendiceal group were found to have metastases. In view of these findings, we wish to re-emphasize the malignant nature of carcinoid tumors, particularly those at nonappendiceal sites.

HISTORICAL RÉSUMÉ

Lubarsch,[29] impressed with the multicentric origin of these tumors of the gastrointestinal tract, their lack of gland formation, the lesser tendency to metastasis, and their cellular dissimilarity to the usual adenocarcinoma of the gastrointestinal tract, separated this group of tumors as an entity. However, he still believed them to be "true carcinomas," and later designated them by the term "little carcinomas."[30] Aschoff and Krompecher both recognized that the tumors presented a distinctive histological picture of a uniform small-cell type. The former author called these tumors "mucous membrane naevi" but pointed out that they might become malignant. The latter pointed out their resemblance to basal-cell carcinomas of the skin. Saltykow, in 1912, suggested that the tumor arose from aberrant cells of the pancreatic islets because of its resemblance to these cells.

The work of Masson and colleagues[19] showed for the first time that intracytoplasmic granules in the cells comprising the tumor had the ability to reduce silver salts. They stated that the tumor cell arose from a well-known type of cell that is normally found throughout the gastrointestinal tract from the stomach to the rectum. It is known by many names—Ciaccio, Schmidt, chromaffin, enterochrome,

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or basigranular cell—but is most frequently called the Nicholas Kultschitzky cell.

Various hypotheses have been formulated about the function of the normal argentaffin cells. Masson and Berger[33] believed that they possessed a neuroendocrine function and that the cells secreted a substance into the periglandular nerve plexus of the intestinal mucosa. Popoff expressed belief that the argentaffin properties of these cells were merely stages in the rejuvenation of functionally exhausted or refractory mucous cells. As to the nature of the granules, Patzelt found a long list of varying opinions expressed in the literature. They were considered to be an exocrine secretion, to have a resorptive function, and to be related to digestion, to the suprarenal medullary cells, the oxyphile cells of the hypophysis, and the pancreatic islet cells.

Stout found that his otherwise typical cases of carcinoid tumor of the rectum did not show argentaffin granules. This appears to have removed any lingering doubt that the affinity for silver is specific to these cells. To explain the difference between carcinoid tumors of the rectum and those occurring elsewhere, he refers to the work of Erspamer. The latter believed that there were several phases in the development of argentaffin cells. In one phase, granules were present but a substance, enteromin, necessary for reduction of silver or chrome salts, was absent. Rectal carcinoids were thereby presumed to be in a pre-enterochrome stage. The chemical nature of the enteromin was believed by Erspamer and colleagues to be an orthodiphenol compound. Jacobson and Simpson postulated that the granules consisted of a pterin and a carbohydrate. More recently Gomori concluded that the cytoplasmic substance responsible for the reduction of silver and chrome salts is resorcinol or a closely related phenolic compound.

Terminology

We prefer the name "carcinoid tumor" despite its deficiencies because of the fact that the silver-staining reaction is not specific to these cells, since the beta cells of the pancreatic islets and others share the argentaffinity many rectal carcinoid tumors have not been shown to reduce silver salts; and chiefly because the name "carcinoid" would emphasize the close relationship between these tumors and the more common carcinomas of the intestinal tract, yet imply some distinctiveness of appearance and clinical behavior. Admittedly, we are using the term in the opposite sense to that for which it was introduced by Oberndorfer, for we believe that these tumors are malignant.

Incidence and Sites of Origin

Appendiceal Group. The most common site of origin of carcinoid tumors is the appendix. They are said to be found in about 0.5 per cent of all surgically removed appendixes.[1] From the Pathology Department of the Boston City Hospital from the years 1910 to 1937 inclusive (Table 1), Porter and Whelan found seventy-two carcinoid tumors in a series of 26,384 appendectomies (0.28 per cent). From this hospital during the years 1938 to 1948 inclusive, there were 47,479 surgical specimens received and in this group there were twenty-eight argentaffin tumors (0.06 per cent).

Table 1

INCIDENCE OF CARCINOID TUMORS

	Porter & Whelan 1910-1937	*Authors 1938-1948*	*Total*
Number of Surgical Specimens	—	47,479	—
Appendiceal	72	25	97
Nonappendiceal	1	3	4
Total Surgically Removed	73	28	101
	1934-1937	*1938-1948*	
Number of Autopsies	2,922	8,699	11,621
Appendiceal	0	1	1
Nonappendiceal	10	28	38
Total Found at Autopsy	10	29	39
Total	83*	57*	140

*One case reported by Porter & Whelan in the 1934-1937 group actually occurred in 1938 (our case 1 in the group from 1938-1947).

Twenty-five of these were found in the appendix. Thus, 97 per cent of carcinoid tumors occurring in surgical specimens were found in the appendix.

The over-all incidence of carcinoid tumors discovered at necropsy has varied from about 1.8 per cent[42] to the figures from this laboratory,[41] which show ten tumors, all extra-appendiceal, in 2922 autopsies (0.34 per cent). Adding our figures to those of this previous report, there has been a total of 38 extra-appendiceal carcinoid tumors in 11,621 autopsies (0.33 per cent) from 1934 to 1948 inclusive. During this period, only one appendiceal carcinoid tumor has been discovered at necropsy.

The discrepancy between the commonest sites of origin in surgical and autopsy material may be partly explained by several factors. The smaller lumen of the appendix is more easily obstructed than is a portion of the small or large bowel by a tumor of the same size. Appendiceal tumors would thereby be expected to give rise to inflammatory signs and symptoms much earlier than nonappendiceal lesions, and hence, would be removed surgically. The much younger age at which appendiceal carcinoid tumors are found compared to that of nonappendiceal tumors would seem to substantiate this hypothesis. The frequency of appendectomy in a general hospital as compared to operations on other portions of the intestinal tract would lead to a greater likelihood of asymptomatic carcinoid tumors being found in the appendix. A not-inconsiderable factor is, possibly, the relatively cursory pathological examination given the appendix at necropsy in contrast to its interest as a surgical specimen.

Nonappendiceal Group. In both surgical and autopsy material, the ileum is the commonest site of origin of nonappendiceal carcinoid tumors. It has been stated[13] that the ratio of appendiceal to ileal sites is about ten to one. In the combined surgical and autopsy series from this hospital, there have been ninety-eight (70 per cent) appendiceal carcinoids in a total of 140 tumors. Twenty-seven (19.4 per cent) have been primary in the ileum or have had at least one of the multicentric sites of origin in this area (Table 2). About 90 per cent of carcinoid tumors in our entire series occurred in the ileal, appendiceal, and cecal regions (Tables 1 and 2). About 64 per cent of our nonappendiceal carcinoids occurred in the ileum. In one report[10] of 92 carcinoid tumors of the small bowel, the ileum was the primary site in seventy-nine (86 per cent) and the lower ileum in sixty-one (66 per cent). Carcinoid tumors of the stomach, duodenum, gallbladder, jejunum, cecum, colon, rectum, mesentery, and Meckel's diverticulum,[4] have been described. Six cases have been listed in which the carcinoid tumor occurred in a teratoma of the ovary.[36]

Four of our tumors were found in the stomach. At least eighteen such tumors (including two of our cases[41]) are on record.[34, 17, 58] Two carcinoid tumors were located in the duodenum. The gallbladder has been the site of origin of three cases[5] including our one case previously reported.[41]

TABLE 2

CARCINOID TUMORS (NONAPPENDICEAL)

Surgical and Autopsy, 1934–1948

Primary site	*No. cases*	*Mult. prim.*	*Metas.*	*Assoc. double prim. malig. tumor*
Stomach	4	1	1	1
Duodenum	2	—	—	—
Gallbladder	1	—	—	—
Jejunum	2	1	1	—
Jejunum & ileum	2	2	1	1
Ileum				
proximal	2	1	1	2
mid-	4	2	1	2
distal	7	1	3	1
unspecified	10	1	4	2
Jejunum, appendix & ileum	1	1	—	—
Ileum & appendix	1	1	1	—
Cecum	1	—	—	—
Cecum & ascending colon	1	1	—	—
*Rectum	2	1	1	—
Undetermined	2	—	2	—
TOTAL	42	13	16	9

*A third previously reported carcinoid tumor of the rectum[29] with generalized metastasis is not included in this report, since it was studied at another hospital.

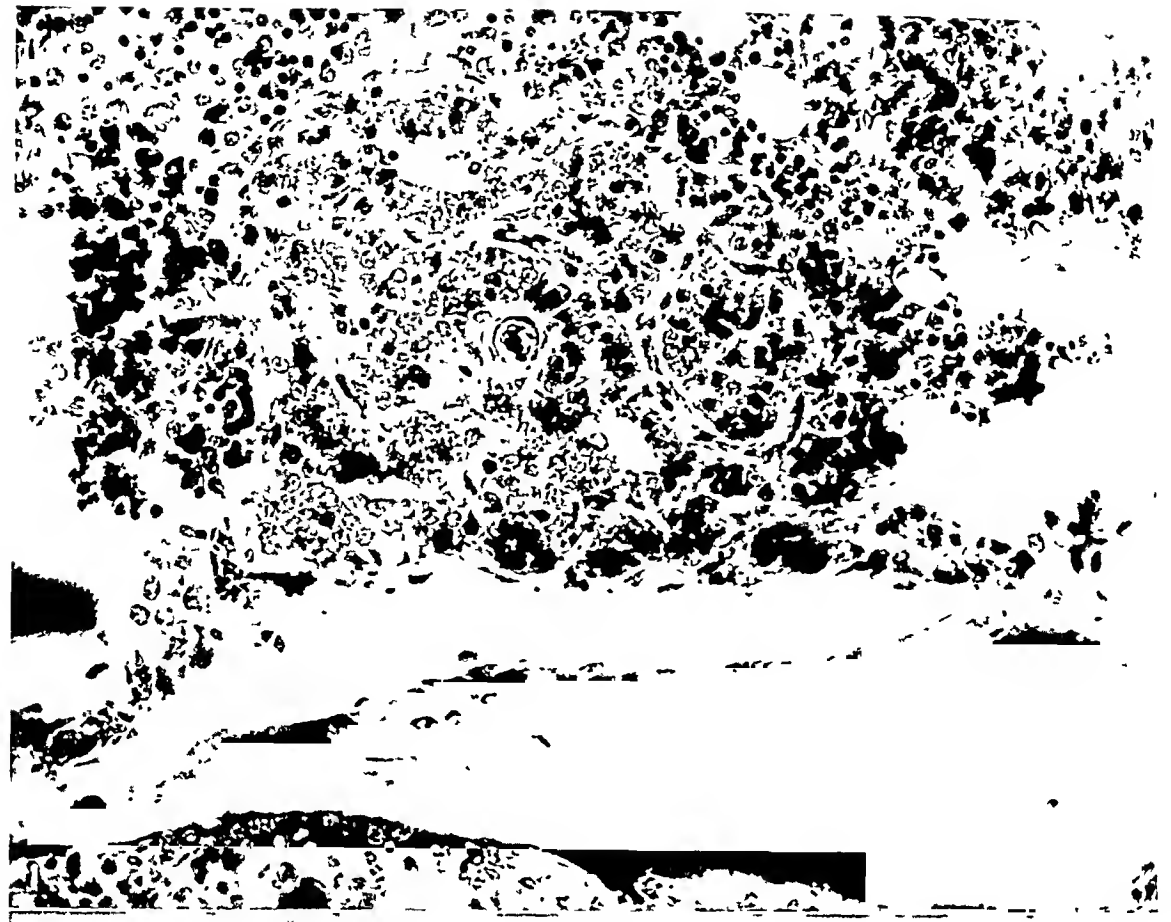

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TABLE 3

CARCINOID TUMORS AND METASTASES

Surgical and Autopsy Tumors Combined

	Porter & Whelan		*Authors*		*Total*		
Primary site	*Cases*	*With metas.*	*Cases*	*With metas.*	*Cases*	*With metas.*	*Per cent*
Appendiceal	72	0	26	0	98	0	0
Nonappendiceal	11	2	31	14	42	16	38
TOTAL	83*	2*	57*	14	140	16	11.4

* See note to Table 1.

One of our cases was localized in the cecum and one had multicentric foci in the cecum and ascending colon. Stout reviewed fourteen carcinoid tumors of the colon and found that four were cecal in origin and ten occurred elsewhere. A thorough review of carcinoid tumors of the colon has been made by Horn who presented seven cases and listed a total of nineteen. Brown et al. added another case. One of our cases occurred in the ileocecal valve, a site predisposing to intestinal obstruction.[22]

Recently, Stout has emphasized the importance of carcinoid tumors of the rectum and reported six cases. Horn has summarized the literature and lists fifty-six cases in the rectum recognized at present. Seven additional cases have been seen by one of us in the referred and routine material at Memorial Hospital. Wilson has also added a case. In all, we have studied ten cases with carcinoid tumor of the rectum[39] but only two are included in this survey. The finding of ten cases in relatively young members of the Armed Forces[15] also suggests that this lesion is more common than realized.

Certain tumors of the bronchial wall (bronchial "adenomas"—carcinoid type) resemble the carcinoid tumors of the intestinal tract and, rarely, show intracytoplasmic argentaffin granules.[21] Their relationship to intestinal carcinoid tumors is undetermined, but their slow growth, low incidence of metastasis, and morphological resemblance to the carcinoid tumor of the intestinal tract, are strikingly similar in many cases.

Multicentric Origin. Thirteen of our forty-two cases showed what appeared to be multiple primary sites of origin (Table 2). Stevenson has reported a case in which there were sixty-eight discrete primary tumors in the ileum. It has been stated[13] that about one third of carcinoid tumors show multiple primary foci.

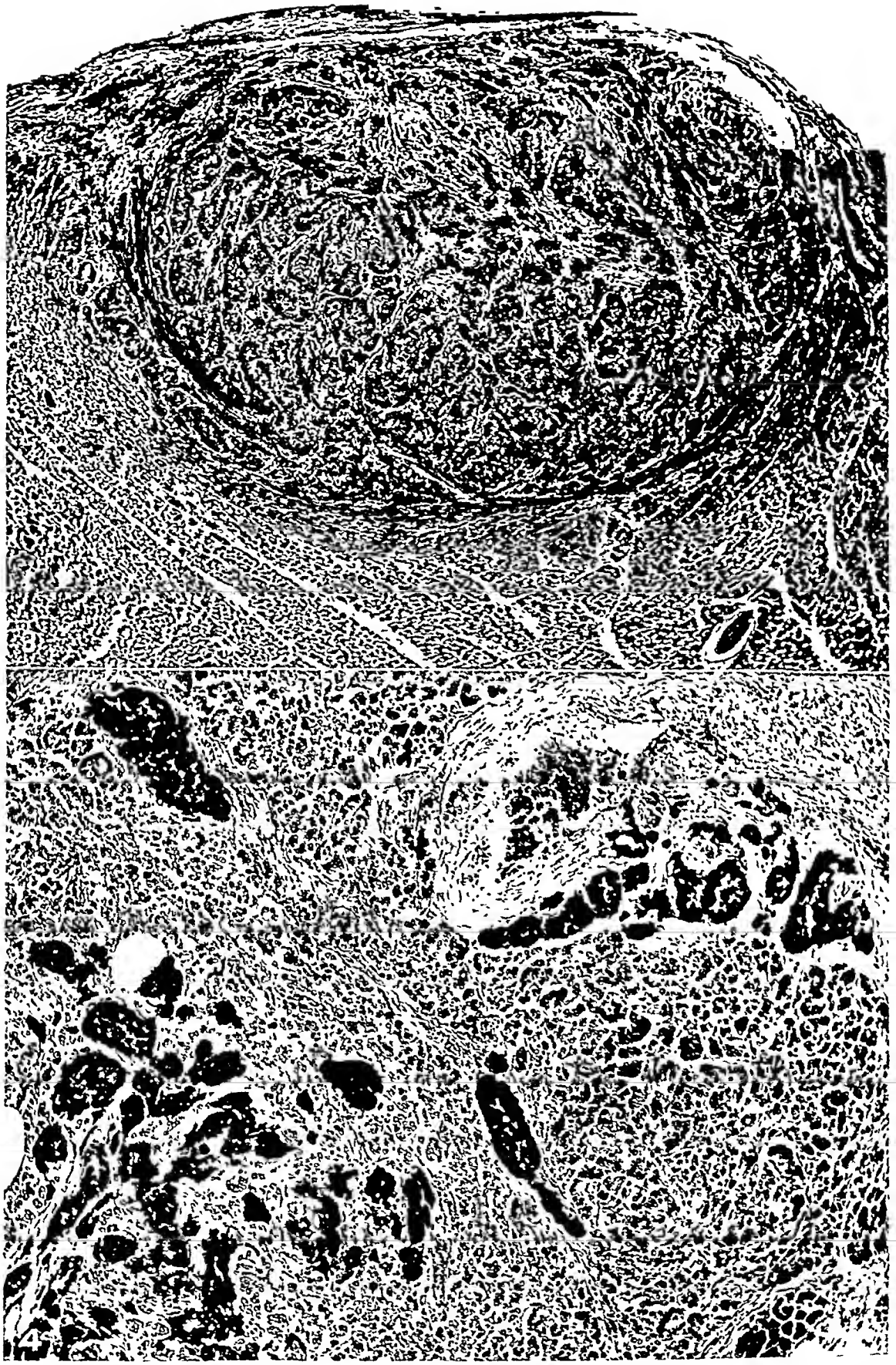
METASTASIS

Ransom is usually credited with first reporting, in 1890, metastasis from a carcinoid tumor, and since then, more than 400 cases have been put on record.[44] The incidence of metastasis is illustrated by a survey of the literature up to 1944,[45] which showed that 126 of 332 carcinoid tumors (37.9 per cent) had associated metastasis. Of our total series of 140 cases (Table 3), surgical and autopsy, appendiceal and extra-appendiceal, sixteen tumors (11.4 per cent) were associated with regional nodal involvement or more distant spread. However, all of the sixteen metastatic lesions occurred in the nonappendiceal primary group of forty-two, so that 38 per cent of this latter group of tumors showed nodal involvement or more distant metastasis.

Extra-appendiceal Metastases. The ileum is the most common site of origin for carcinoid tumors associated with metastasis. In a group of sixty-eight "malignant" tumors collected

FIG. 1. *Case 20. Metastatic carcinoid tumor in the vertebral marrow. (Phloxine–methylene blue. × 500.)*

FIG. 2. *Case 20. Metastatic carcinoid tumor nodule in the interventricular septum of the heart. Septum sectioned sagittally and the apex reflected anteriorly.*



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from various authors,[35] the distribution of the primary sites was as follows: stomach, one; jejunum, two; ileum, thirty-nine; small bowel (unspecified), nine; appendix, fourteen; and colon, three. "Malignant" carcinoid tumors are said[12] to comprise 23 per cent of all malignant neoplasms affecting the small bowel. In the present series, eleven of the sixteen tumors with metastasis arose in the ileum, or if multicentric, one site of origin was the ileum. Forty-one per cent of the tumors arising in the ileum were associated with metastasis (Table 2). It is of interest that Lubarsch's first two cases[29] showed serosal involvement.

Reports of twenty-six cases of carcinoid tumors, primary in the large bowel, were reviewed by Stout. Of the four arising in the cecum, all were "malignant." At least eight metastasizing carcinoid tumors of the cecum are on record.[1, 22] Horn found that ten of nineteen carcinoid tumors of the colon showed nodal involvement or metastasis. One of our cases arose in the cecum, and one case showed multiple sites of origin in the cecum and colon—both were unaccompanied by metastases.

Seven of sixty-four tumors arising in the rectum, known to us, were associated with metastasis[22, 39, 57] including one of the two cases of rectal carcinoid reported herein, one found in the files of Memorial Hospital and not previously reported, and a third previously reported from another hospital.[39]

In the present series of four carcinoid tumors arising in the stomach, one showed metastasis. This is the fourth such case with metastasis in a total of eighteen known cases. None of the three gallbladder tumors was associated with metastasis. In two of our cases, metastatic but no primary intestinal lesions were found.

Appendiceal Metastases. The relative infrequency of metastatic lesions accompanying carcinoid tumors primary in the appendix as compared to a significantly high percentage of metastases with nonappendiceal primary lesions is well known. However, at least twenty-three cases of carcinoid tumors of the appendix with metastatic lesions have been reported,[1, 44] and one had occurred at the age of 16 years.[42] Since we believe with others[6, 8, 9, 12, 29] that nonappendiceal carcinoid tumors are malignant, and we cannot distinguish the appendiceal from the nonappendiceal carcinoid tumor morphologically, we believe that it is rational to consider appendiceal carcinoids to be malignant. The low incidence of associated metastasis is thought to be related to the very slow growth of the tumor and the structural peculiarities of the appendix which lead to the removal of the tumors before metastasis occurs.

TABLE 4

METASTATIC SITES

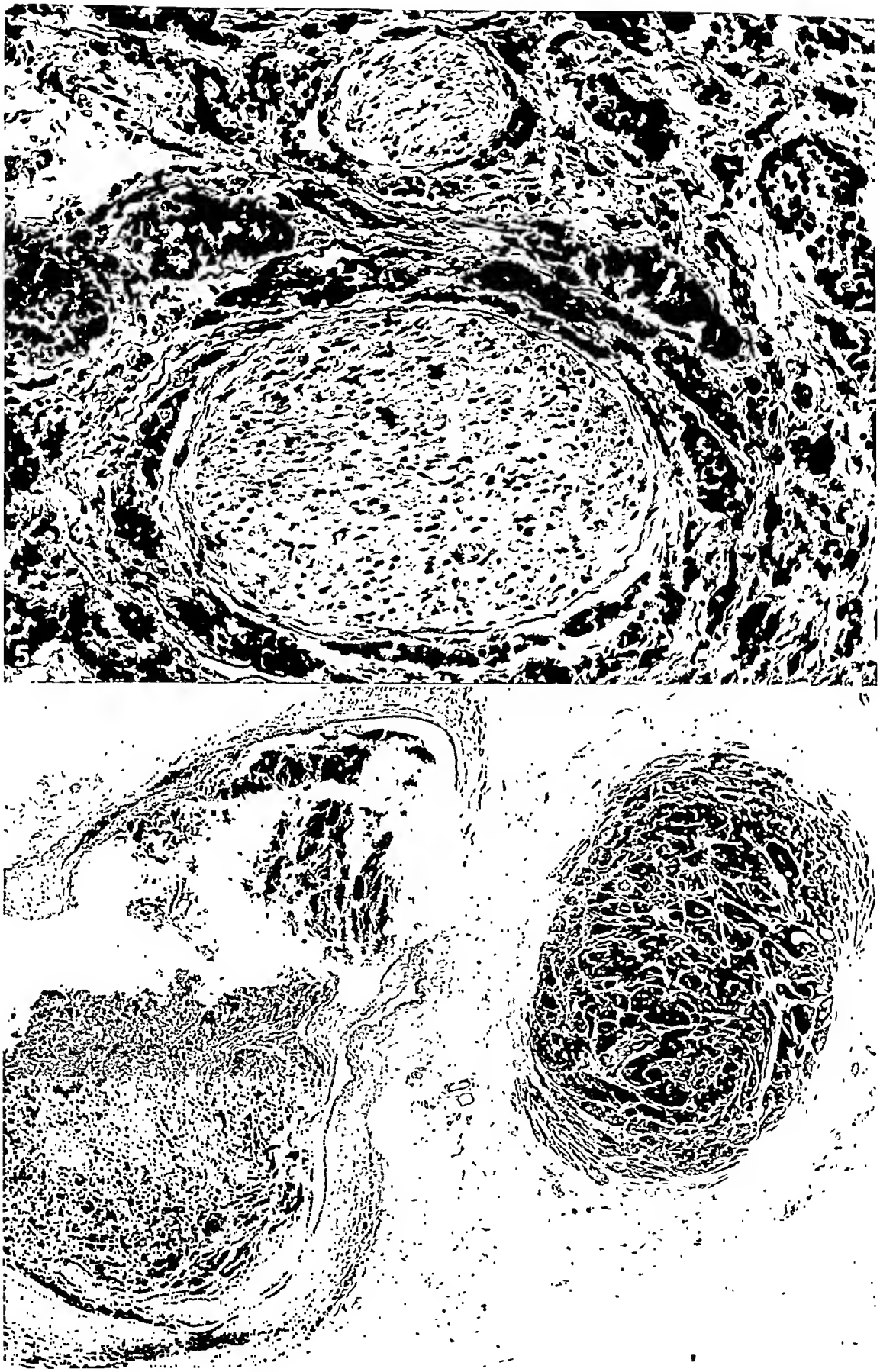
16 Cases

Mesenteric nodes	9
Liver	6
Serosa of bowel	5
Omentum	4
Distant nodes	4
Regional nodes	3
Bone (vertebral)	2
Heart, Pancreas, Spleen, Kidneys, Adrenals, Ovaries	each 1

Metastatic Sites. In our series of sixteen malignant tumors (Table 4), involvement of the mesenteric nodes occurred in nine cases, of the liver in six, of the intestinal serosa in five, of the omentum and distant nodes in four cases each, and in the regional nodes in three cases. Two cases showed metastasis to vertebral marrow (Fig. 1). The following organs were involved once: heart (Figs 2, 3), pancreas (Fig. 4), spleen, kidneys, adrenals, and ovaries. In twenty-one carcinoids, primary in the small bowel, metastases were

FIG. 3. *Case 20. Metastatic carcinoid tumor nodule in the myocardium. (Phloxine–methylene blue. × 125.)*

FIG. 4. *Case 20. Demonstration of argentaffin granules (black areas) in a carcinoid tumor metastatic to the pancreas (nonislet area). (Bodian's protargol stain. × 200.)*



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present in the regional nodes in eleven instances, in the liver in eight, and in the serosa of the intestines in three.[10] Widespread metastases have been reported to the peripancreatic, para-aortic and mediastinal lymph nodes, liver, pancreas, and heart,[53] lungs, the spleen,[45] kidneys, brain, bone marrow, left flank, and subcutaneous tissues of left axilla and right shoulder,[55] testes and peritoneum,[11] and dura.[27] One of our cases (case 20) showed mesenteric, peripancreatic, and regional-node involvement and metastases to the heart, spleen, liver, pancreas, adrenals, ovaries, and bone marrow (Figs. 1 to 4).

It is thus apparent that although local lymphatic spread is the more common route of metastasis (Fig. 5), invasion of the vascular channels must occur in some cases. We have seen tumor invasion of mesenteric arteries and large veins in two of our cases (Fig. 6).

Associated Malignant Tumors

Our autopsy material from 1938 to 1948 shows that nine (31 per cent) of the twenty-nine carcinoid tumors found were associated with a malignant tumor of different histological type (Tables 2 and 3). It is of interest to compare these autopsy findings with the reported incidence of double primary malignant tumors. This incidence has varied from 3 to 8 per cent.[48] Although no associated malignant tumors were found in the ten carcinoid tumors found at autopsy in this laboratory from 1934 to 1937, the occurrence of nine cases with associated malignant tumors in the total of thirty-nine cases comprising both groups is 23 per cent, still a relatively high value. A much larger number of cases will have to be collected to determine the significance of these figures. Of additional interest is the occurrence of multiple primary tumors of the intestinal tract (mouth to anus), which has been reported[48, 52] as about 7.7 per cent. Since six of the nine noncarcinoid malignant tumors were in the intestinal tract, our incidence of double primary malignant tumors in the intestinal tract is 15.8 per cent. Dukes[14] observed that three of his nine carcinoid tumors of the rectum were discovered in surgical specimens containing carcinoma of the rectum. At least five cases have been reported,[2, 12, 23, 54] wherein the carcinoid tumors have been associated with a secondary primary carcinoma, and two of these[23, 54] had a third, independent carcinoma.

All of our patients with double primary malignant tumors were in the sixth, seventh, or eighth decades, a fact that might partially account for our high incidence of double tumors, since the carcinoid tumor is, in general, relatively slow growing and presumably would be compatible with a longer life span, thereby allowing greater possibility for a second tumor to occur.

All but one of the associated malignant tumors in this series were carcinomas. One adenocarcinoma of the lung and one adenocarcinoma of the prostate were present. One malignant lymphoma—a plasmacytoma—was present with involvement of one ovary and many lymph nodes. No associated malignant tumor was present in the same part of the intestinal tract as the carcinoid tumor. Two epidermoid carcinomas were observed, one of the tongue and one of the pharynx. One adenocarcinoma of the stomach and three adenocarcinomas of the colon were also present. No malignant lesion was found associated with the four carcinoid tumors of the large bowel (two rectal, one cecal, and one in the cecum and ascending colon).

Of the nine cases in which a second primary malignant tumor was found, six occurred in cases in which there were either multiple primary areas of carcinoid tumor, metastases, or both. Three of the cases with a double primary tumor occurred in association

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Fig. 5. *Case 20. Mesentery. Perineural and connective tissue lymphatic invasion by a carcinoid tumor, primary in the terminal ileum. (Phloxine–methylene blue. × 400.)*

Fig. 6. *Case 15. Cross section of a mesenteric artery and vein, both of which display carcinoid tumor thrombi. (Phloxine–methylene blue. × 20.)*

TABLE 5

CARCINOID TUMORS—NONAPPENDICEAL—(1938–1948)

Case	*Age*	*Sex*	*Location of primary tumor*	*Size of primary tumor*	*Metastases*	*Associated malignant tumors*	*Clinical signs and symptoms*
1. (A-38-193)	61	M	Distal ileum	3×1.5×0.8 cm.	Serosal wall & mesentery	——	None
2. (A-39-198)	72	M	Distal ileum	0.5 cm.	None	——	None
3. (A-39-271)	73	F	Mid-ileum	1.0 cm.	None	Epidermoid ca., pharynx	None
4. (A-39-421)	63	F	Ileum	0.5 cm.	None	——	None
5. (A-39-776)	62	M	Distal ileum	0.5 cm.	None	Adenoca., prostate with metas.	None
6. (A-40-756)	61	M	Ileum	1.0 cm.	None	Ca., lung	None
7. (A-40-927)	60	M	Stomach	1.0×0.5 cm.	Mesenteric nodes	——	None
8. (A-41-141)	72	F	Mid-ileum	1.0×0.8 cm.	None	——	None
9. (A-41-208)	64	M	Mid-ileum	0.2 to 0.4 cm. (multiple)	None	——	None
10. (A-41-327)	61	M	Jejunum	0.8 cm.	None	——	None
11. (A-41-603)	73	M	(?)	(?)	Serosa of small & large bowel & lesser omentum	——	None
12. (A-41-670)	71	M	Ileum	0.1 to 1.2 cm. (multiple)	Serosa & adjacent mesentery	Adenoca., stomach; metas. to liver	None
13. (A-41-819)	65	M	Distal jejunum & ileum	0.3 to 0.7 cm. (multiple)	None	Epidermoid ca., tongue	None
14. (A-41-860)	88	M	Proximal ileum	2.5 cm.	Omentum (3.5 cm.)	Ca. (in situ), descend. colon	None
15. (A-42-66)	74	F	Distal ileum	Annular obstructing	Mesentery; regional node; liver	——	Progressive constipation to obstipation
16. (A-44-493)	73	M	Stomach	0.3 to 0.5 cm. (multiple)	None	Ca., sigmoid; metas. to liver	None
17. (A-45-318)	77	M	Cecum and ascend. colon	0.3 to 0.5 cm. (multiple)	None	——	None
18. (A-45-457)	63	M	Distal ileum	0.3 cm. (multiple)	None	——	None
19. (A-45-461)	61	M	Distal ileum	1.0 cm.	None	——	None
20. (A-47-104)	47	F	Distal ileum (ileocecal valve)	2.0 cm.	Mesentery, regional nodes, liver, pancreas, peripancreatic nodes, heart, spleen, ovaries, adrenal & bone marrow	——	Emaciation, weight loss, diarrhea, ascites; (but also had cirrhosis of liver)
21. (S-47-284)	45	F	Rectum	Annular constricting (multiple)	Liver, kidney, regional & paravertebral nodes	——	Progressive constipation, rectal bleeding
22. (S-47-2445)	69	M	Rectum	2.0×1.5 cm.	None	——	Black stools

TABLE 5 (*Continued*)

Case	*Age*	*Sex*	*Location of primary tumor*	*Size of primary tumor*	*Metastases*	*Associated malignant tumors*	*Clinical signs and symptoms*
23 (A-47-473)	61	F	Proximal ileum	0.5 cm (multiple)	None	Adenoca., descend. colon	None
24. (A-47-693)	73	F	Ileum	1.0×1.5 cm.	Mesenteric nodes	—	None
25 (A-48-118)	55	M	(?)	(?)	Liver, para-aortic nodes	—	Bloating, weight loss, anorexia
26. St. Mgts. (S-47-71)	80	M	Ileum	Annular constricting	Omentum	—	Chronic abdom. distress—then acute obstruction
27. (A-48-153)	80	F	Distal jejunum	0.2 to 0.6 cm (multiple)	Liver	—	Diarrhea, weight loss
28 (A-48-236)	70	F	Mid-ileum	0.2 to 1.8 cm (multiple)	Serosa of bowel, mesenteric nodes	Malignant lymphoma (plasmacytoma)	None
29 (A-48-504)	63	M	Duodenum (first part)	1.0 cm	None	—	None
30 (A-48-527)	76	M	Jejunum & ileum	0.2 to 2.0 cm (multiple)	Serosa of bowel & adjacent mesentery	—	None
31. (A-48-665)	63	F	Cecum	0.5 cm	None	—	None

with carcinoid tumors of multicentric origin. One case with associated double primary malignant tumor showed metastasis from a solitary carcinoid primary tumor. Two cases occurred in the presence of both a multicentric primary carcinoid tumor and metastasis of the latter.

CLINICAL DATA

Age and Sex. Carcinoid tumors are said to occur in all decades of life, the earliest being reported in an infant, 10 days old.[35] Appendiceal carcinoid tumors are usually discovered with the highest frequency in the third decade and those of the small intestine in the fifth and sixth.[50] In twenty-nine cases, the average age at which appendiceal carcinoid tumors were discovered was 25 years, and for similar tumors of the small bowel the average age was 55 years.[42] Carcinoid tumors showing metastatic lesions usually occur in the fifth decade or later.[19] Of thirty-seven patients with "malignant" carcinoid tumors whose age was known, only two were less than 40 years of age.[41] The patients in this series having nonappendiceal carcinoids are tabulated in Table 6, according to age in decades. It can be seen that most of our cases occurred in the seventh and eighth decades. The incidence of metastasis roughly paralleled the incidence of the tumor, although both the youngest and the oldest cases, 37 and 88 years respectively, showed metastatic lesions. The average age of all of our patients with nonappendiceal carcinoid tumor was 66⅔ years. Those with metastatic lesions averaged 66 years; those without metastasis, 68 years.

TABLE 6

CARCINOID TUMORS (NONAPPENDICEAL)

Age Incidence

Decade	*No.*	*With metas.*	*Remarks*
30–39	1	1	Youngest (with metas.), 37 yrs.
40–49	4	2	
50–59	2	1	
60–69	20	3	
70–79	12	7	
80–89	3	2	Oldest (with metas.), 88 yrs.
TOTAL	42	16	

There was a slight preponderance of males (twenty-six) over females (sixteen) in our series. Metastatic lesions were noted in about the same ratios—in ten of twenty-six cases in males, and in six of sixteen in females.

Signs and Symptoms. Carcinoid tumors of the appendix frequently produce obstruction of this organ or inflammatory reaction, either one of which leads to the signs and symptoms of acute appendicitis.

The signs and symptoms most commonly associated with small-bowel carcinoid tumors are those of intestinal obstruction. In the first case reported by Lubarsch[29] there was stenosis of the bowel wall with almost complete obstruction. In one series[23] of 152 cases, thirty-six (24 per cent) showed signs of obstruction. In another[10] of 115 cases from the literature, it was found that twenty (17 per cent) had obstructive signs. Because of their mode of spread, the so-called "malignant" lesions are more likely to give signs and symptoms. By contiguous growth and interadherence to the serosa of adjacent loops of bowel, they may cause kinking of the bowel and subsequent obstruction. In Cooke's series, seven of ninety-four "benign" lesions produced partial or complete obstruction, whereas thirteen of twenty-one "malignant" lesions gave obstructive features. None of the fourteen nonmetastasizing tumors of the ileum in our combined series gave signs or symptoms; they were all incidental autopsy findings. Four of the nine ileal carcinoids with metastasis produced varying degrees of obstruction. Diarrhea and weight loss occurred in two other cases, one jejunal, and one ileal in origin. And in one case, metastatic to liver and para-aortic nodes, but without a discernible primary lesion, weakness and weight-loss were present. In twenty-nine lesions of the small bowel, seven, therefore, gave clinical evidence of their presence.

Horn found that thirteen of seventeen colon carcinoid tumors, on which there were clinical data, gave symptoms, but they could not be distinguished from those of carcinoma of the colon, clinically. Brown et al. added another case of carcinoid tumor of the cecum in which the patient had symptoms suggestive of carcinoma. Neither of our two cases occurring in the colon gave signs or symptoms.

Both of the rectal tumors in our series gave signs or symptoms of either obstruction or bleeding. Ten of thirty-two cases of rectal carcinoid tumor reviewed by us[39] gave symptoms, usually rectal bleeding and difficulty with bowel movements.

Thus of the total of forty-two nonappendiceal tumors from this laboratory, nine (21.4 per cent) produced signs and symptoms. All were accompanied by metastatic lesions. Nine of the sixteen tumors with metastasis gave clinical evidence of their presence, whereas none of the twenty-six nonmetastasizing tumors were apparent clinically. Carcinoid tumors of the stomach, duodenum, and gallgladder were asymptomatic in our small series. Eight of the eighteen reported cases with gastric carcinoids gave signs or symptoms, including two cases with massive hemorrhage.[34, 47, 58] The gallbladder carcinoid tumors were associated with no signs or symptoms in two cases; one instance was discovered in a case of cholecystitis with cholelithiasis.[5]

Diagnosis

In the diagnosis of small-bowel carcinoid tumors, Miller and Herrmann emphasize the value of roentgenographic findings that tend to differentiate these tumors. Kinking of the small bowel plus the absence of a tumor mass in the lumen is thought by them to be highly significant. They were able to diagnose one case preoperatively by such features. Grimes and Bell call attention to the most common signs and symptoms noted in carcinoid tumors of the small bowel—intermittent episodes of small-bowel obstruction associated with abdominal pain, diarrhea and weight loss.

Preoperative diagnosis of carcinoid tumor of the appendix cannot be made at present with any degree of assurance, since the signs and symptoms associated with the presence of the tumor are those of acute appendicitis. The difficulties of differentiating, clinically, carcinoid tumor from adenocarcinoma of the

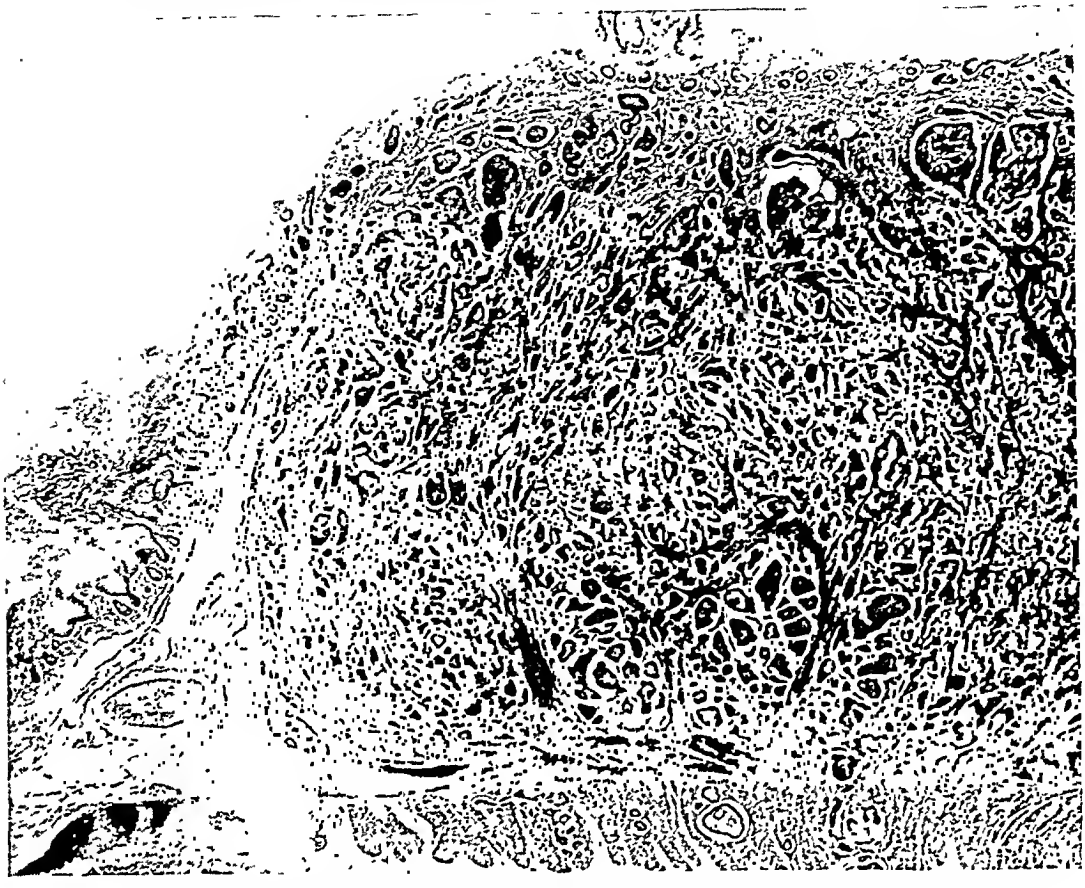
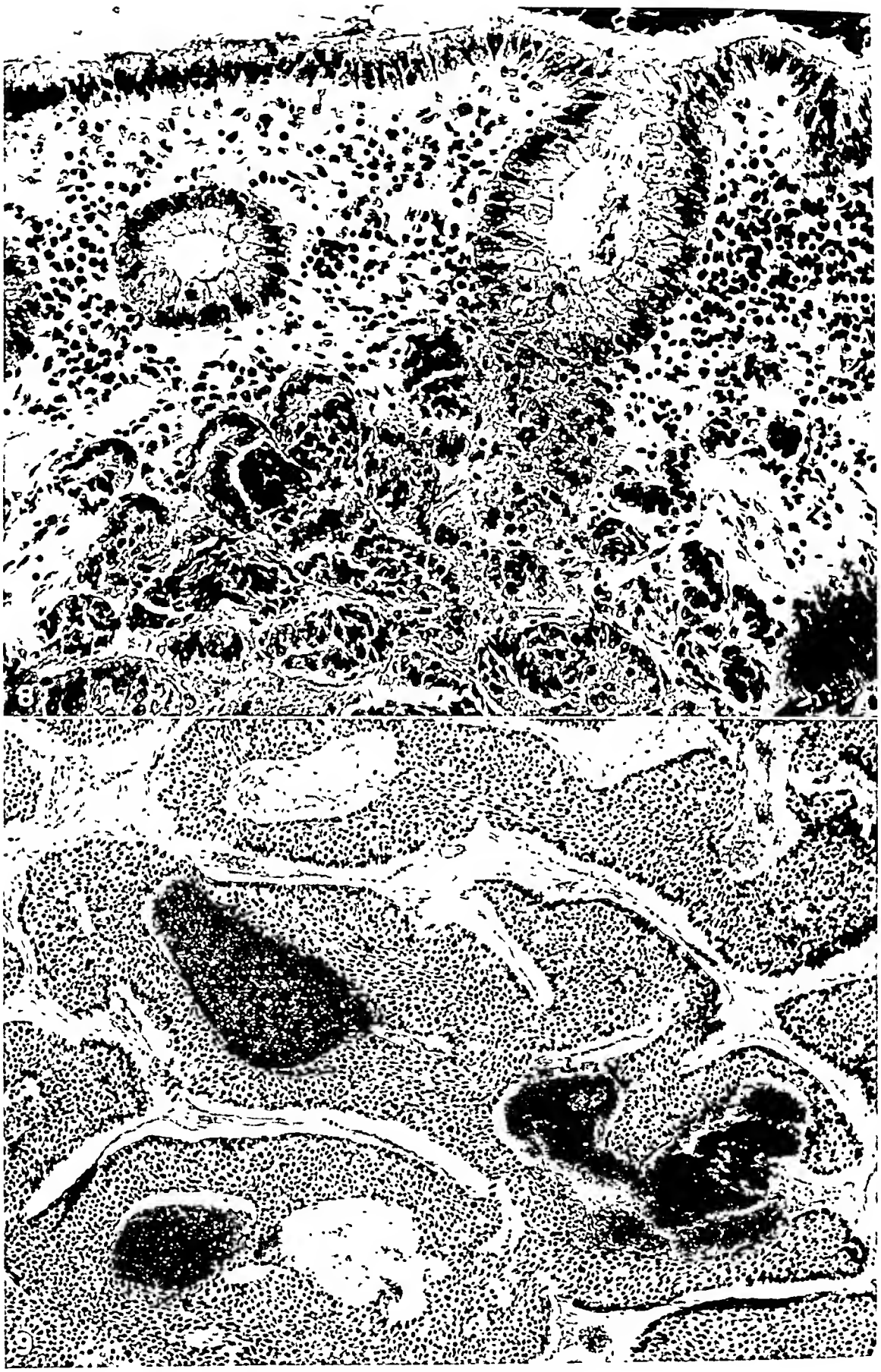


FIG. 7. *Case 10. Submucosal carcinoid tumor of the jejunum with intact but displaced mucosa, a fibrous supporting stroma, and invasion of the muscular coat by nests of carcinoid cells. (Phloxine–methylene blue. × 70.)*

rectum and submucosal nodules of that area have been emphasized.[24, 39] Not enough is known of carcinoid tumors in other areas to indicate that there is anything distinctive in their behavior whereby they could be clinically differentiated from adenocarcinoma or other neoplasms of the gastrointestinal tract. Horn found no clinical features of carcinoid tumors of the colon that would enable one to differentiate them from carcinomas of that organ.

GROSS APPEARANCE

In the appendix, carcinoid tumors are usually present at the distal end of the organ, and when well developed, they appear as bulbous swellings. Sections through the appendix at this point usually show the lumen to be obliterated by a firm mass of pale yellow, gray, or brown tumor. The mucosa often, and the muscular layer usually, are intact although either may be replaced by tumor. Carcinoid tumors of extra-appendiceal origin usually arise in or near the terminal ileum. They appear as one or more submucosal, yellow or gray-yellow, nodules covered by intact mucosa. There may be partial intraluminal narrowing or extension through the wall of the bowel. Kinking of the bowel by contiguous serosal growth of two adjacent loops may give rise to intestinal obstruction. Three tumors in our series, two ileal and one rectal, were annular constricting growths. One caused progressive obstruction; the second contributed to an acute obstruction when a foreign body became impacted in the narrowed lumen of the bowel; and the third, the rectal, was associated with increasing



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constipation. All were accompanied by metastases. Usually the nonappendiceal lesions were described as submucosal nodules, polyps, or occasionally, papillomas. Intestinal mucosa adjacent to the tumor was most often described as intact (Figs. 7, 8, 11). Primary lesions varied from 0.1 to 3.0 cm. in largest diameter and averaged about 1.7 cm. The color of the cut section of the primary lesion was listed in nineteen nonappendiceal cases: eight were said to be white, gray-white, or gray; six were described as gray-yellow; two were tan or tan-white; two were brown or dark red-brown; and one was gray-green. Metastatic lesions were most frequently described as gray or gray-white. All lesions were said to be firm except the metastatic liver lesions of one (case 15), which had "cystic degenerative areas in the center." These tumors (Fig. 9) showed the blood-filled cysts lined with carcinoid cells occasionally seen in these tumors. Rectal lesions most commonly occur in the anterior wall, are usually solitary nodules partly covered with mucosa, average about 1.0 cm. in diameter, and the cut surface frequently is yellow.[39]

Microscopic Appearance

Masson[32] has thoroughly studied the histology of carcinoid tumors of the appendix. He describes the typical cell as a small epithelial cell with an oval or round nucleus that has a well-defined nuclear membrane and a fine stippling of chromatin. The cytoplasm is usually palely acidophilic, granular, and often finely vacuolated. The cell membrane is indistinct and many cells appear to blend into a column with no apparent delineation of their cytoplasm (Fig. 10). In general, three cell types have been described —round or polygonal, palisade, and columnar. They may form columns, nests, coils, or amorphous masses of cells. Occasionally rosettes or pseudorosettes are formed. The cytoplasm contains cholesterol as evidenced by the doubly refractile Maltese cross, seen by polarized light, fat by the osmic acid and Sudan stains, and possibly some lecithin by Ciaccio's stain. Characteristically, acidophilic granules are present in the cytoplasm. The argentaffin and chromaffin properties of some of these granules has been mentioned. Dr. F. B. Mallory, from this laboratory, demonstrated that these granules also have an affinity for lead and are therefore plumbophilic as well. Horn has shown the presence of mucin by the mucicarmine stain.

The stroma of the tumor is composed of fibrous or hyaline connective tissue with a rich vascular supply of fine capillaries, and reticulum, nerve, and elastic fibers.

Some variations from the general pattern described occur. The characteristic type of growth is that of multiple cords, columns, and nests of uniformly regular, small, round cells having very little cytoplasm, although in the rectum, and occasionally elsewhere, the columns of cells frequently are narrow and interwoven, giving the appearance that has been likened[51] to carelessly coiled festoons of ribbons (Fig. 11). Even in this distinctive pattern, there are intermingled the other types of cells previously described. In some metastatic lesions we,[39] as others,[17, 45] have observed large, cystic, blood-filled spaces whose walls contain small, cuboidal, carcinoid tumor cells (Fig. 9).

The problem of determining whether the tumor is "malignant" or "benign" by the usual histological criteria is complicated by the fact that in appendiceal carcinoids, which usually show no evidence of nodal or metastatic lesions, one frequently sees invasion of submucosa, muscle, and serosa. Lymphatics are often found that are filled with tumor, even though the cells may be uniformly small, round, and show none of the usual signs of

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Fig. 8. *Case 22. Carcinoid tumor of the rectum. Normal rectal mucosa showing carcinoid cells closely associated with rectal gland. (Phloxine–methylene blue. × 400.)*

Fig. 9. *Case 15. Section from a metastatic carcinoid tumor nodule in the liver showing the cystic blood-filled spaces occasionally seen in these tumors. (Phloxine–methylene blue. × 100.)*

For captions see opposite page.

atypism commonly associated with malignant neoplasms (Fig. 7). Even in carcinoid tumors growing in metastatic foci, the tumor cells look benign from the standpoint of the usual cytological criteria. However, very careful search of many histological sections of metastatic foci reveals some abnormalities of nuclear and nucleolar size and shape that are consistent with the usual cytological criteria of malignant neoplasms. On the other hand, to attempt to predict whether a carcinoid tumor would show metastasis as judged by histological criteria on the basis of a few sections is very difficult. We have seen two deaths from generalized metastasis within two and a half years after the onset of symptoms from carcinoid tumors of the rectum, and in each case one could find anaplastic cells in only a few foci.[39] We regard all carcinoid tumors as malignant although usually very slow growing.

Illustrative Cases
(see table 5)

Case 15 (*A42-66*). This was a carcinoid tumor of the ileum with progressive small-bowel obstruction, mesenteric lymph-node invasion, and metastasis to the liver.

The patient was a 74-year-old white woman with elevated blood pressure who had had repeated cerebral vascular accidents over a 6-year period For several years before entry to the hospital, she had lived in a nursing home and had required enemas for relief of constipation. Months before entry, the constipation became worse, and for ten days prior to hospital entry she had had no bowel movements. She died about thirty hours after admission to the hospital. The clinical diagnoses were repeated cerebral thromboses and intestinal obstruction.

At autopsy, in addition to cerebral thromboses, there was marked distention of the duodenum, jejunum, and ileum. The bowel loops contained large amounts of brown, fluid, fecal material. Eighteen centimeters proximal to the ileocecal valve was a firm, annular, constricting lesion narrowing the lumen to less than 1 cm. There were tumor masses in the adjacent serosa and mesentery and several white tumor nodules in the regional nodes and liver. Histological sections showed most of the tumor to be a typical carcinoid, and in some areas the tumor nodules grew in the blood-filled cystic pattern (Fig. 9) described previously. Tumor thrombi had completely occluded some mesenteric vessels (Fig. 6).

Increasing constipation and slowly progressive small-bowel obstruction by an annular constricting lesion were the features of this case.

Case 26. This was a carcinoid tumor of the ileum with acute intestinal obstruction and mesenteric lymph-node invasion.*

The patient was an 80-year-old white man who had been under observation by his physician for six months because of repeated bouts of gaseous distress and pain in the right lower abdomen. During this period, the patient twice had gastrointestinal roentgenographic studies, each time with findings of slight compression of the lower ileal loops in the right lower quadrant by a nonadherent extrinsic mass. A mass was palpable in this region.

Several hours before admission, the patient had a sudden onset of right lower abdominal pain, and he vomited several times. On admission to the hospital, physical examination showed an elderly, acutely distressed man with severe abdominal pain and distention. Laparotomy was performed soon after entry and a firm, baseball-sized mass was found in the mesentery to which some loops of ileum were adherent. A 70-cm. segment of small bowel containing the tumor and adjacent mesentery was resected, and a primary anastomosis of the small bowel performed. The patient did well and was discharged on the seventeenth hospital day.

*We are indebted to Dr E E O Neil and Dr G K Mallory for the data on this case, which was operated upon at St Margaret's Hospital, Dorchester, and examined pathologically at the Mallory Institute, Boston City Hospital, Boston, Massachusetts

Fig. 10. *Case 11. Typical growth pattern of a carcinoid tumor invading the muscular layer and serosa of the ileum Note the cytoplasmic granularity, indistinct or absent cell membranes, and suggestion of rosette formation.* (*Phloxine–methylene blue.* × *950.*)

Fig. 11. *Case 22. Carcinoid tumor of the rectum. Intact edematous rectal mucosa overlying tumor. Narrow columns of tumor cells resembling coiled festoons of ribbons.* (*Phloxine–methylene blue.* × *120.*)

PATHOLOGICAL EXAMINATION. In the mid-portion of the 70-cm. segment of small bowel were two areas where the bowel was firm and white, and the lumen narrowed markedly. On opening the proximal loops of bowel, evidences of obstruction were present and at the point of most marked luminal narrowing there was an impacted prune stone. The wall at this point was thickened to 0.8 cm. and was white and hard on section. The mucosa was intact throughout. In the mesentery adjacent to these areas was an oval mass measuring 5×4×3 cm., which was in continuity with the ileal masses in two places. On section, the tumor was homogeneous, firm, gray-yellow, and had a definite fibrous capsule about it. Microscopically, the tumor was composed of typical cords and sheets of carcinoid cells, which infiltrated the submucosa, muscularis, serosa of the bowel, and the mesentery but did not appear to disturb the mucosa over the tumor masses.

This was a case in which the fortuitous blocking by a foreign body of an already narrowed lumen of the small intestine brought to sudden focus a case of intermittent, low-grade intestinal obstruction, which had undoubtedly been present and progressive over a long period of time.

Case 20 (*A47-104*). This was a carcinoid tumor of the ileum with metastases to the mesenteric nodes, liver, heart, spleen, pancreas, ovaries, adrenal, and bone marrow.

The patient was a 47-year-old white woman who entered the hospital because of progressive weakness, swelling of the ankles and abdomen, marked weight loss, and bouts of nonbloody diarrhea. A history of alcoholic intake of several-years' duration was obtained. The patient remained in the hospital for five days, during which time an abdominal paracentesis yielded 4 liters of bloody fluid. The patient rapidly failed and died on the fifth hospital day.

At necropsy, ascites was present as well as cirrhosis of the liver, alcoholic type, with diffuse metastases from a carcinoid tumor of the ileum. The primary tumor was present in the terminal ileum overlying the posterior wall of the ileocecal valve, elevating the mucosa and partially occluding the valve lumen. The adjacent bowel wall was infiltrated by tan-colored tumor tissue. Similar tumor tissue was present in the adjacent mesentery and regional nodes, and extensive metastases were present in the liver, pancreas (Fig. 4), heart (Figs. 2, 3), spleen, adrenal, ovaries, and vertebral bone marrow (Fig. 1).

The case shows the extensiveness of metastatic lesions in contrast to the more frequent discovery of carcinoid tumors with only regional-node involvement. The presence of cirrhosis of the liver obscures the evaluation of the importance of the metastatic lesions in the causation of signs and symptoms.

Case 21 (*S47-284*).* This was a carcinoid tumor of the rectum with metastases to the liver, right-kidney region, and para-aortic lymph nodes.

A 45-year-old white woman entered the hospital complaining of nausea, vomiting, and constipation for one month prior to entry. This was the fourth of a similar type of episode which had occurred in the previous ten months. Sigmoidoscopic examination revealed an annular constricting mass on the posterior wall, 14 cm. from the anal sphincter. The mass was hyperemic and bled easily upon touch. Biopsy of the lesion showed it to be a carcinoid tumor.

At abdominal exploration, a large, firm, fixed mass was palpable in the terminal rectum and tumor nodules were present in the liver, right-kidney area, and in the para-aortic nodes. Colostomy was performed, and the patient discharged after an uneventful recovery. It was learned that during the twenty months following operation, the patient had persistent nausea and vomiting, was severely debilitated, and passed blood by rectum. She died at home two and a half years after the onset of signs and symptoms of her illness. An autopsy was not obtained.

In this case, the obstructive bowel signs and symptoms were the early prominent features, and no history of rectal pain or bleeding was elicited until later in the course of the disease. This case of carcinoid tumor of the rectum with death about thirty months after onset of symptoms emphasizes that not all carcinoid tumors can be considered as slow-growing.

Case 22 (*S47-2445*).† This was a carcinoid of the rectum, probably noninvasive, and producing clinical symptoms.

The patient was a 69-year-old white man who had had black stools, nausea, and vomiting for one week prior to entry. A similar episode had occurred six weeks previously. Sigmoidoscopy revealed a small polyp, 1.5

*This case has been published in more detail elsewhere.[39]

†Reported elsewhere in more detail.[39]

cm. in width and 2 cm. long, with a small, pedunculated base on the left and the anterior walls of the upper rectum or rectosigmoid junction. Histological examination showed the tumor to be a polypoid structure with a typical carcinoid-cell structure (Figs. 8, 11). There was no invasion of the stalk or the adjacent rectal wall. Ten months later, the patient was entirely symptom-free and sigmoidoscopic examination of the original biopsy site showed no evidence of recurrence.

This case illustrates the difficult problem involved in considering proper therapy for carcinoid tumors of the rectum. One has to balance the known potential for metastasis against the probability of completely excising the tumor, as well as considering the mortality and discomfort associated with extensive rectal surgery.

Two patients previously reported from this laboratory[41] gave symptoms attributable to the presence of a tumor mass or its metastases. One was a 67-year-old man who had constipation, flatus, and belching for one year. He had noted a mass in the right lower quadrant for six months with diarrhea, which alternated with constipation. Weakness and a weight loss of 15 pounds occurred. Surgical exploration revealed a complete intestinal obstruction caused by a carcinoid tumor of the ileum, which had extended to the base of the mesentery and bound the ileum into a completely obstructing mass. The second case was that of a 65-year-old man who had anorexia and constipation for four months. There was abdominal pain after meals and a 40-pound weight loss in four years. Necropsy revealed a carcinoid tumor of the ileum and appendix with metastases to the peritoneum, mesentery, omentum, liver, pancreas, distant nodes, and vertebral marrow.

The first case illustrates obstruction of the bowel by mesenteric kinking and binding—the signs emphasized by radiologists. The second presented nonspecific signs and symptoms associated with many types of abdominal neoplasms.

Therapy

It is generally agreed from both clinical experience and histological observation that these tumors are slow-growing, both at the site of origin and in the metastatic lesions.

The plan of choice in the treatment of carcinoid tumors appears to be surgical resection of the tumor and as much of its metastatic spread as is feasible. Noninvasive tumors should also be removed because of their known metastatic potentialities and because in some cases obstruction, often of sudden onset, may develop. Removal of as much of the tumor as possible may permit a prolongation of life, oftentimes symptom-free, for many years. A case has been reported[31] in which a small-bowel carcinoid tumor was removed together with a portion of the tumor in the adjacent mesentery. Some tumor masses were left at the base of the mesentery and yet twenty years later when death occurred from an unrelated cause, necropsy revealed the same tumor masses as partially calcified nodules at the base of the mesentery. Another case[56] was characterized by an obstructing tumor at the ileocecal junction, which was relieved by an ileocolostomy. The primary tumor and its many metastases were not removed because they were believed to be inoperable. Ten years later the patient died of intercurrent disease, and at necropsy, no appreciable growth of the tumor or its metastases was found. One of the cases previously reported from this laboratory[41] had a primary tumor of the ileum removed, but many lymph nodes, presumed to contain metastatic carcinoid tumor, were not disturbed. The patient was alive and well ten years later. Dockerty, Ashburn, and Waugh[13] report eight patients living ten months to nineteen years postoperatively, even though some had hepatic metastases at operation.

Reports of these isolated cases should not be construed as evidence that any carcinoid tumor may be judiciously ignored. On the contrary, we have observed some cases that died with generalized metastases within a few years after the onset of symptoms. However, the slowness of growth is the rule and surgical excision seems advisable even in cases that would be considered to be inoperable by the usual standards of neoplastic surgery.

It hardly seems necessary to mention the

importance of frozen-section diagnosis of metastatic lesions at operation, since a nodule or two in the liver or other organ seen at operation might lead to the defeatist attitude that the primary lesion was inoperable. If the pathologist reported that the tumor was a carcinoid, it would seem justifiable to us to perform surgical excision of the primary and the metastatic lesions, including those in the liver, in view of the little information available about the course of these tumors and the reports of long survivals after palliative or no specific treatment.

In rectal polypoid tumors, it would appear that solitary, freely movable lesions in young patients may be excised locally and the patients observed frequently for evidences of recurrence or invasion. In obviously infiltrating or annular constricting rectal lesions, the treatment should be similar to that used in adenocarcinoma of the rectum. Cases between these two extremes require considerable investigation, clinically and pathologically, and only after a large number of cases have been assayed can one be certain as to definitive therapy.

Radiation therapy of carcinoid tumors has received only scant attention. We have been able to find only a few isolated observations on irradiation of these tumors.[2, 7, 26] The reports suggest that this type of tumor and its metastatic lesions may be radiosensitive. Undoubtedly, the slow rate of growth of many of these tumors would tend to make these reports of lesser significance. Brown et al. radiated lymph nodes, left behind after a primary carcinoid tumor was excised, with 500 r daily for six days. Two months later, the nodes were removed surgically. No radiation effect was noted on the tumor cells in the nodes. More such observations on the effect of radiation are needed before adequate appraisal of this type of therapy can be made.

Summary

1. A series of 140 carcinoid tumors from the files of the Mallory Institute of Pathology was reviewed. Ninety-eight tumors were found in the appendix, forty-two were of nonappendiceal origin.

2. The most common sites of origin of carcinoid tumors are respectively the appendix, distal ileum, and cecum; approximately 90 per cent of the tumors reviewed herein were from this region.

3. We believe that all carcinoid tumors should be considered malignant, albeit appendiceal carcinoids rarely show metastasis, and those of other areas may be very slow-growing. Metastases were present in 38 per cent of the present series of nonappendiceal carcinoid tumors. Of the carcinoid tumors discovered at autopsy, 23 per cent also showed a second malignant tumor of noncarcinoid type.

4. Clinical signs and symptoms of small-bowel carcinoid tumors are usually those of slowly progressive, or intermittent intestinal obstruction, but acute obstruction may develop. Rectal carcinoid tumors give rise to bleeding and constipation in some cases. Carcinoid tumors with widespread metastasis give no signs and symptoms distinct from those of any widespread neoplastic process.

5. Treatment consists of resection of the primary tumor and as much of its metastatic growth as is feasible. Such procedures are at times followed by many years of symptom-free existence. The use of radiation has not been fully explored in the therapy of these lesions.

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Hemangiopericytoma

A Study of Twenty-five New Cases

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IN 1942, in collaboration with Dr. Margaret R. Murray, the writer published a study of nine tumors for which the name "hemangiopericytoma" was suggested. A year later another case was reported with Dr. Cassel. These were all vascular tumors featured by a proliferation of capillaries; surrounding these were massed spindle-shaped or rounded cells somewhat in the fashion of the vessels and cells of the glomus tumors but without the highly organoid architecture and encapsulation of that spectacular neoplasm or the remarkable number of nerves and the paroxysmal attacks of pain associated with it. By means of tissue culture, Dr. Murray had demonstrated that the characteristic cells of the glomus tumor, called "epithelioid" by Masson, were probably identifiable as derivatives of the cells with long branching processes applied to outer walls of capillaries named "pericytes" by the Swiss histologist Zimmermann. Although these cells have no myofibrils, they have contractile powers and have been assumed to have some kind of relationship with smooth-muscle cells. It occurred to the writer that the rounded and spindle-shaped cells of these peculiar tumors, which had hitherto apparently been called vascular fibrosarcomas or passed unnoticed, might also be derivatives of the pericyte, and without any real scientific basis in support, the tumor was christened "hemangiopericytoma."

The writer has been disappointed that no other group studies of this tumor type have been published so that it might have been established first, whether or not it is a definite entity, and second, but less important, whether the name selected is justified or should be abandoned in favor of something else. Since the task has not been undertaken by anyone else, it was decided to use the material accumulated in this laboratory for the purposes of such a study. Through the kindness of sixteen different individuals in various localities in North America, twenty-five additional cases have been collected that seem to have the characteristics of this tumor. There are three others that surely belong to the group, but that, because of inadequate data, poor stains, or other reasons, have been excluded so that the picture may be as sharply defined as it is possible to make it. Since it has been necessary to collect material from so many different sources, obviously this must be a very uncommon tumor, and the writer is most grateful to all those who sent him the cases and were kind enough to permit him to use them.

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HISTOLOGICAL APPEARANCE

When one first undertakes to unravel the complex histological pictures exhibited by this tumor, the task seems hopeless, for the variations appear endless. The cells are not uniform in size or shape, the formation of connective-tissue fibers is variable—sometimes none among the tumor cells, sometimes a few, occasionally many are formed—and the blood vessels may be hard to detect. There is only one relationship that is constant; in all the tumors, there is a profuse proliferation of obvious or occult capillaries, each one surrounded by a thin or thick connective-tissue sheath, outside of which are the characterizing tumor cells that vary so much in their appearance. In parts of some tumors, even the capillaries may seem to disappear, although never in all parts of any given tumor. After one has become familiar with these tumors, it may be possible to identify them with some assurance from the hematoxylin-

and-eosin stain alone, but diagnosis is made much easier if a satisfactory silver connective-tissue–fiber stain is used, for this will blacken the sheaths of the capillaries and make them easy to recognize, and it will also demonstrate the fact that the tumor cells are outside of that sheath. This extravaginal position of the cells enables one to differentiate this tumor from the hemangioendothelioma in which the characteristic tumor cells are found inside of the capillary sheath.

Why is it that this tumor form should show such marked and confusing variations? They can be explained if the hypothesis regarding the nature of the pericyte can be accepted. It has been supposed that the pericyte is in some fashion related to the smooth-muscle cell. If this is true, there should be tumors showing cells without myofibrils but suggesting the appearance and arrangement of smooth-muscle cells, there should be other tumors whose cells suggest the appearance of the epithelioid cells of the glomus tumor but without its organoid arrangement, and between these two extremes one may expect to find tumors whose cells show all gradations of possible variations in shape, size, and arrangement. The question of the variability of the number and thickness of the connective-tissue fibers in these tumors can easily be accounted for if it is recalled that almost any derivative of the mesenchyme can lose its specificity and take on fibroblastic activity.

The perivascular orientation of the pericyte derivatives is generally inconspicuous in this tumor type because there is usually no interruption in the continuity of the cells filling the space between one capillary and another; in this respect, it differs from most glomus tumors in which continuity is interrupted by a loose stroma packed full of nerve fibers. This fact makes recognition more difficult but helps to save one from confusing these tumors with others that have a perivascular orientation of their cells, such as paragangliomas and many other endocrine tumors. The histological appearance of these tumors, however, is such that they will not often be confused with epithelial neoplasms.

Because it is of paramount importance to display the various histological appearances demonstrated by this tumor, this feature will be discussed first and in some detail. Wherever possible, each case has been illustrated by photomicrographs both of sections stained with hematoxylin and eosin and also with Laidlaw's silver reticulin stain. The magnification in every instance except for case 23 is the same, namely 515 diameters. It has not been deemed necessary to use lower magnifications because in each instance the variations from any given field are of relatively minor degree and importance. Some attempt has been made to group the cases to facilitate microscopic description, but this has not been strictly adhered to, for sometimes other considerations seemed to alter the listing.

The microscopic descriptions will not be given in detail for each case, but a running account made of the whole group. Case 1 (Fig. 1)* is a frankly vascular tumor in which the vessels have distinct, thick walls composed of concentrically layered, plump, spindle-shaped cells, which are in the position of smooth-muscle cells but have no myofibrils. Actually, these are not veins but capillaries with a thick collagenous sheath, and the cells in question are outside of this sheath and have a considerable number of connective-tissue fibers between them. In some instances, the spindle-shaped cells are not layered but simply lie outside the capillary sheath without any definite arrangement. Thus in this case, we have a vascular tumor with cells that imitate smooth-muscle cells in position and arrangement but that are not smooth-muscle cells. Case 25 (Fig. 20) from a dog's leg is quite similar except that often the vessel lumina have vanished leaving only a bit of collagen in their stead, and the layering of the surrounding cells has been exaggerated so that some vessels (not shown in the illustration) are enormous. Case 2 (Fig. 2) is a compound nevoid sort of tumor composed of fat, connective tissue, and vascular elements. These latter consist of small groups of

*Because the number of pages required for illustrations exceeds the number devoted to text, the figures have been placed all together at the end of the article.

capillaries with reticulin sheaths surrounded by spindle-shaped cells, similar to those found in case 1, which show some tendency to be concentrically layered about the lumina, but the latter are so closely placed that the surrounding cells intermingle and orderly arrangement is lost. This seemingly represents a step toward the disorderly arrangement found in the majority of hemangiopericytomas. These three tumors, then, can be regarded as featuring cells approximating the appearance of smooth-muscle cells.

Cases 3 and 4 are at the other end of the scale, and feature cells that more nearly resemble the appearance of the epithelioid cells of the glomus tumor but that do not have its organoid appearance. Case 3 (Fig. 3) shows a diffuse, rich sprouting of capillaries lined with prominent endothelial cells and surrounded by a scattering of rounded cells, which sometimes cling to the capillary wall and sometimes lie free outside it in the finely fibrillated stroma either as units or in small groups of three or four cells surrounded by delicate reticulin fibers. Since these capillaries do not have continuous reticulin sheaths, the silver stain is most confusing. The resemblance of this tumor to the infiltrating glomus tumor explanted in vitro and illustrated in the paper on glomus tumor by Murray and Stout is striking. It represents a glomus tumor that has lost part of its organoid characteristics but retained the shape and orientation of its pericytes. Case 4 (Fig. 4) both in its primary form and recurrent manifestations retains the rounded form of its cells and the rich proliferation of its capillaries which form a meshwork; but the cells solidly fill in the space between the capillaries and the latter, since they seldom have patent lumina, can often be detected only by their endothelial lining cells with the hematoxylin-and-eosin stain, although silver blackens the reticulin sheaths and makes them strikingly apparent.

These first five cases are important because they show the two extremes of the tumor cells, which tend to simulate smooth-muscle cells in cases 1, 2, and 25, and glomus epithelioid cells in cases 3 and 4. All the rest of the tumors show variations between these two extremes. It must be remembered in looking at the illustrations that in most instances formalin has been the fixative, and the preparation and staining has frequently left much to be desired. The discriminating reader will detect these imperfections and, I trust, discount the evidences of distortion, shrinkage, and poor staining that even the best and most careful photography cannot hide. The writer craves pardon for these faults; he has nevertheless persevered in reproducing the pictures because the difficulties of assembling such a collection as this all properly fixed and stained within a single lifetime seem insurmountable.

In cases 5 and 6 the vascular spaces are generally dilated and therefore obvious, and there are very few reticulin fibers among the cells. (Fig. 5.)

Cases 7, 8, 9, and 10 (Figs. 6, 7, 8, 9) are all tumors in which the lumina of the capillaries are only potential spaces that are filled with the lining endothelial cells. The silver reticulin stain shows the very great numbers of these capillaries, and it also demonstrates that there are very few reticulin fibers among the tumor cells. Cases 7 and 8 are malignant tumors.

Cases 11, 12, 13, 14, 15, 16, and 17 (Figs. 10, 11, 12, 13) are closely related to the foregoing two groups in so far as the rich capillary meshwork is concerned. This is obvious in ordinary stains when the lumina are patent but difficult to detect if, as in case 13 (Fig. 12), there are no lumina. What distinguishes this group is the fact that there are often many delicate reticulin fibers between the cells.

The next three cases, 18, 19, and 20 (Figs. 14, 15), show another variant, which is most marked in case 20 (Fig. 15), namely, a thickening of the reticulin sheaths of the capillaries. It may be remarked that this thickening of the capillary wall is not an indication of the benign nature of the tumor. On the contrary, this tumor was sufficiently large and aggressive to lead to amputation through the thigh; it should be compared with case 9 in the 1942 paper by Stout and Murray, which showed a similar thickening of the capillary walls and proved its malignancy by metastases. That case was important for it demonstrated not

only that the hemangiopericytoma may be malignant and metastasize, but also that the same tumor can assume quite different histological aspects.

Cases 21, 22, and 23 (Figs. 16, 17, 18) are all proved malignant tumors. It is unfortunate that no silver reticulin stains are available for cases 21 and 22, but their histological appearance after hematoxylin-and-eosin staining seems so much like many of the other cases that no doubt about them exists in the writer's mind. Case 23 is remarkable because it developed in the ileum and metastasized only to the liver. The cells in this case are definitely anaplastic and have a malignant aspect; those of the other two are so much like the cells in nonmetastasizing tumors that no definite differences have been detected.

Case 24 (Fig. 19) is of interest because it represents the development of one of these tumors in the meninges. It is just like the majority of the others and bears no resemblance to any form of the common meningiomas.

Case 25 (Fig. 20) has been placed by itself because it represents the occurrence of one of these tumors in a dog.

Only one of these tumors was explanted in vitro and studied by Dr. Margaret R. Murray. Although the tumor cells grew easily and profusely, Dr. Murray does not feel that it showed sufficiently distinctive characteristics to warrant exact identification of the cells. This was a keen disappointment, for had it been possible to classify the cells as pericytes, it would have furnished strong support of the hypothesis that these are vascular tumors featuring pericytes.

Clinical Data

Clinical data have been compiled from the nine cases previously published by Stout and Murray, the tumor reported by Stout and Cassel, and the twenty-four human cases included in the present report. The sex of thirty-three patients is known: sixteen were males and seventeen females. The ages at reported onset varied from birth to 81 years. The spread is shown in Table 1.

The anatomical distribution of these tumors is sufficiently wide in the thirty-four human cases to warrant the belief that one may look for them wherever capillaries are found. The majority, however, have occurred in the superficial soft tissues chiefly in the subcutaneous and muscular layers. There were twenty-three of these as follows: head and neck, six; trunk, five; upper extremity, six; and lower extremity, six. Five more were found in the retroperitoneal, mesenteric, and omental tissues, and one each in the following locations: orbit, tongue, pericardium, diaphragm (extending into pleural space), ileum, and meninges. The writer has also seen an unreported tumor in the uterus.

The tumors have varied very greatly in size. Many of them have been small, but in eleven the mass has exceeded 8 cm. in diameter (cases 5, 7, 8, 16, 18, 19, 20, 21, and 22 of the present group, case 9 published by Stout and Murray, and the omental tumor reported by Stout and Cassel). The tumors have usually been firm, apparently circumscribed, and often nodular. Except in the very few instances in which the tumor has been in the skin, there has been no external discoloration or redness to suggest its vascular nature. Even when excision was attempted, marked vascularity of the tumor or its immediate environs was noted in only eighteen of the thirty-four cases; however, it is only fair to state that the clinical data about many of the other cases is very meager and it is possible that more of them may have shown this feature. The fact that the tumor itself so infrequently has shown visible evidence of its vascular nature is not

Table 1

AGES AT REPORTED ONSET OF 32 HEMANGIOPERICYTOMAS

Congenital	*Years*								
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	81
3	4	3	5	4	6	2	3	1	1

surprising when one notes how frequently the lumina of the capillaries are only potential spaces and even when they are patent, they very seldom contain red blood cells. Calcification in the tumor mass was noted in cases 5, 7, and 12, but actual necrosis of the tumor tissue is apparently rare. In the majority of these cases, the tumor, clinically, has often appeared encapsulated. Actually this has seldom been confirmed microscopically, for the supposed capsule usually contains tumor formations. However, this infiltration has been limited, and if the tumor has been removed with its capsule, recurrence has been uncommon.

It is very difficult to form an accurate opinion about the speed of growth. Several times it has been very slow indeed. The omental tumor reported by Stout and Cassel was known to have been present for at least sixty years and possibly many more. Other examples of very long duration are: Stout and Murray—case 6, twenty-four years; case 7—thirty-one years; and in the present series —case 5, fifteen years and case 15, thirty-eight years. On the other hand, the known duration of the majority has usually been measured in months and was seldom more than three years.

Very unfortunately, follow-up information about most of these cases is so often lacking entirely that it is extremely difficult to form an accurate opinion as to their degree of malignancy. There is definite proof of malignancy in six patients: cases 7, 8, 21, 22, and 23 of the present group and case 9 of the Stout and Murray series. Two of these originated in the thigh, two in the retroperitoneum, one in the mesentery, and one in the ileum. Seven other tumors showed aggressive growth without known metastases. Two of them died because of the tumor (case 11 in the orbit, and case 24 in the scalp and meninges); five others (cases 3, 4, 12, and 19 of the present series and case 8 previously reported by Stout and Murray) recurred one or more times because of incomplete excisions. These were situated in the finger, the tongue, the retroperitoneum, and two in the popliteal space. The recorded sites of metastases in the six cases are as follows: bones, three; liver, two; and one each in the following tissues: lymph-node, lung, peritoneum, retroperitoneum, and subcutaneous. Most of the malignant tumors were either relatively large or in situations where complete removal was difficult or impossible, and most of them were in elderly people although there was one 11-year-old boy (case 21). No tumor known to have been congenital is known to have been malignant. Radiotherapy was used for the metastases of case 9 of the Stout and Murray series and for presumed persisting retroperitoneal tissue in case 19 of the present series. No conclusions can be drawn from the available data.

Case Reports

Case 1. (P & S 22967.) Female; age ? (A.I.P. 121266.)

A mass, thought to be an enlarged lymph node, was noted in the lower part of the left side of the neck for eight years. Recently it enlarged. When excised it measured 2×1.5 cm. and appeared pale brown and fibrous (Fig. 1.)

Case 2. (P.H.-S.P. 98095. Hist. 824377.) Female; age, 2 years.

When the child was 8 months old, a swelling was noted in the left arm. It increased in size slowly and painlessly. She was admitted to Babies Hospital and a mass 3×4×2 cm. was removed from the lower medial aspect of the arm just above the lower end of the humerus. It was irregular, firm, subcutaneous, and fixed to the skin but not the deeper structures. Grossly, it appeared to be composed of nodular fat. The case was not followed after the wound healed. (Fig. 2.)

Case 3. (P & S 25340.) Male; age, 44 years. (Institute of Path. Anat., Univ. of Montreal, 1565, Dr. Pierre Masson.)

The patient had an egg-sized tumor in the popliteal space without adhesions or involvement of bone, joint, or muscles. It was excised but recurred locally and was re-excised twice during the next two years. (Fig. 3.)

Case 4. (P & S 23270 and 24894.) Male; age, 13 years. (R. B. Green Hospital, San Antonio, Texas, S-45-34 and S-46-83, Dr. A. O. Severance.)

A 1×1 cm. mass had been noted in the dorsum of the tongue near the foramen caecum for four months. It was excised, re-

curred locally, and fourteen months later a second excision was done. (Fig. 4.)

Case 5. (P & S 22754.) Female; age, 47 years. (A.I.P. 117863.)

This woman had complained of tenderness over the medial aspect of the left lower leg for fifteen years. A mass appeared which increased in size more and more rapidly during the last two years. When excised, it was roughly ovoid, measured 11×8.5×7 cm. and involved all of the tissues between the skin and the periosteum but did not involve the latter. There were large blood sinuses in and around the tumor. The rest of the tumor seemed fibrous and there were areas of calcification.

Case 6. (P & S 24067.) Male; age, 65 years. (*Southern Baptist Hospital*, New Orleans, La., S-45-2505, Dr. E. H. Lawson.)

This is a tumor of the triceps muscle, of three-months' duration. (Fig. 5.)

Case 7. (P & S 26861, 27723.) Male; age, 68 years. (Ellis Fischel State Cancer Hospital, Columbia, Mo., Dr. L. Ackerman.[1])

The patient had had right lower-quadrant pain, constipation, and abdominal enlargement for an unstated length of time. The roentgenogram showed an abdominal mass with calcification at the level of the twelfth rib posteriorly and to the right of the vertebral column. On exploration, an apparently encapsulated mass, weighing 1020 gm., lay between the right kidney and adrenal and was excised. It appeared cellular with areas of hemorrhage, necrosis, and calcification. Ten months later, there was a mass palpable in the epigastrium, and a roentgenogram showed a metastatic nodule in the right lung. No treatment was given. The patient died fifteen months after operation. (Fig. 6.)

Case 8. (P & S 23292.) Female; age, 81 years. (Ellis Fischel State Cancer Hospital, 45-7118, Drs. Lauren Ackerman and R. E. Johnson.)

This woman had lost 60 pounds in weight and two weeks prior to admission had had a massive hemorrhage per rectum. Examinations were all negative except for a movable mass, 5×2.5 cm., in the right lower quadrant. At operation, a grayish-purple nodule 8×6×4 cm. was removed from the mesentery of the jejunum. It was surrounded by multiple, translucent, peritoneal implants. Four months later, the woman died and there was no autopsy. (Fig. 7.)

Case 9. (P.H.-S.P. 74920. Hist. 506250.) Female; age, 5 years.

This little girl was studied in the Vanderbilt Clinic. Several months before admission she had been pinched on the medial side of the left upper arm. A small area of ecchymosis appeared but no attention was paid to it until one month before admission when a nodule appeared which enlarged slightly. It was excised. Because of an erroneous pathological diagnosis of fibrosarcoma, the scar was re-excised fifteen days later. (Fig. 8.)

Case 10. (P & S 26744.) Female; age, 74 years. (St. Francis Hospital, Miami Beach, Florida, BA-6-1947, Dr. R. J. Poppiti.)

A disc-shaped tumor, 5×5×0.5 cm., was found in the anterior leaflet of the pericardium near the base. The cut surface was firm, buff-colored; there were several gray, fibrous-tissue septa. It had a thick, gray, hyalinized capsule and there was an associated sanguino-fibrinous pericarditis. (Fig. 9.)

Case 11. (P & S 20745 and 21896.) Female; age, 66 years. (Case of Dr. Andrew A. Eggston: see Plate XV facing p. 747 and Fig. 415, p. 771.[2])

This woman had a vascular tumor which is reputed to have started in the ethmoid sinus and invaded the orbit, eventually filling the entire orbit and completely enclosing the globe. It was operated upon four times during seven years. She died about one month after the last operation, which was exenteration of the orbit. The sections are from the third and fourth operations. (Fig. 10.)

Case 12. (P & S 28932.) Male; age, 35 years. (A.I.P. Acc. 213843.)

A mass appeared in the left popliteal region. There was no roentgenographic evidence of bone involvement, but there was spotty calcification in the soft-part mass. It was excised but recurred locally in six months: seventeen months after the first operation, it was again excised. It was reputed to have been firm, bosselated, and attached to deep structures. (Fig. 11.)

Case 13. (P.H.-S.P. 61108. Hist. 489732.) Female; age, 25 years.

Two years before, a tiny nodule appeared, which painlessly increased in size until it measured 12 mm. in diameter. It lay in the subcutaneous tissue over the middle of the infraorbital ridge. It was excised. It was a solid circumscribed mass that, on section, had a smooth gray surface. (Fig. 12.)

Case 14. (P.H.-S.P. 87629. Hist. 726425.) Female; age, 43 years. (Dr. B. P. Watson, Sloane Hospital, New York.)

A slow-growing, kidney-shaped, subcutane-

ous swelling had slowly enlarged the mons pubis for seven years. When excised, it measured 7 cm. in diameter and was exceedingly vascular. Five years and eight months later, there was no evidence of recurrence.

Case 15. (P & S 27852.) Male; age, 48 years. (Dr. B. F. Stout, Stout-Todd Laboratories, San Antonio, Texas.)

A 5×5×3 cm. subcutaneous tumor was removed from the occipital region, where it had been present for at least thirty-eight years. The cut surface showed a hemorrhagic appearance with cystic spaces and diffuse yellowish areas. There was no recurrence after fifteen months.

Case 16. (P.H.-S.P. A4431. Hist. 856487.) Female; age, 23 years.

Because of ankle swelling following an induced abortion, she had consulted a doctor ten months before, who examined her chest with a fluoroscope and told her there was something there. Two attacks of dull pain in the left chest following bending to that side, and increase in size and breadth of finger tips had occurred. On admission, roentgenographic examination showed the heart displaced to the right and a dense shadow in the region of the left diaphragm.

At operation, by Dr. Herbert Maier, the lower half of the left pleural cavity was occupied by a large, very vascular, brownish-red tumor springing from the dome of the diaphragm; it was also adherent in four places to the inferior borders of the lung. The whole left leaf of the diaphragm contained enlarged vessels. The tumor was excised, and the specimen measured 17×12.5×7.5 cm. There was no evidence of recurrence six months later; after this she left the country and could not be traced. (Fig. 13.) Tissue from this case was explanted in vitro and studied by Dr. Margaret R. Murray. The tumor cells grew readily, but Dr. Murray does not feel that it showed sufficiently distinctive characteristics to warrant exact interpretation.

Case 17. (P & S 23126.) Male; age, 43 years. (Dr. E. B. Kaplan.[3])

The tumor, in the palm of the left hand between the interosseous fascia and ulnar bursa, was excised. There was no recurrence in four and a half years.

Case 18. (P & S 26336.) Female; age, 50 years. (M & S Hospital, San Antonio, Texas. Pathologist: Dr. A. O. Severance. Surgeon: Dr. J. B. Williams Seguin.)

A mass had been present for two years in the left scapular region. It was painful when pressed against. The excised specimen measured 10×6.2×3.5 cm. It was apparently encapsulated, was soft and rubbery with a very vascular, grayish-brown, cut surface. Two years and three months later, there was no evidence of recurrence. (Fig. 14.)

Case 19. (P & S 29205.) Colored female; age, 47 years. (Yonkers General Hospital. Pathologist: Dr. Milton J. Eisen.)

The patient came because of indefinite soreness in the lower abdomen of several-days' duration. Pelvic examination revealed a soft tumor mass to the left of the uterus. A grayish-yellow, soft, very vascular and cystic mass, measuring 8.5×7.8×6.7 cm., was removed from around the lower part of the ureter. Excision was deemed incomplete and three months later a total of 7200 r measured in air was given, divided into twenty-four doses, through multiple ports during a two-months' period. This reduced but did not completely eliminate some thickening at the site of operation.

Case 20. (P & S 28603.) Male; age, 45 years. (A.I.P. Acc. 212564.)

A painful swelling developed in the outer part of the thigh and grew rapidly. After a month, roentgenographic examination showed no evidence of bone involvement. A very vascular subcutaneous tumor was biopsied, and shortly after, the lower extremity was amputated. The tumor measured 16×7×10 cm. and lay within the vastus lateralis with the fascia about the muscle forming a pseudocapsule. The tumor extended into the fascia lata at the site of excision. (Fig. 15.)

Case 21. (P.H.-S.P. 83465, Babies Hosp. S-1033. Hist. 470660.) Male; age, 11 years.

The patient was first admitted to Babies Hospital, November 12, 1935 because, during a routine physical examination, a mass was felt in the left lower quadrant. It seemed hard and fixed and could be palpated through the rectum. Exploration was by Dr. E. J. Donovan, November 18. A very large, very vascular, retroperitoneal tumor occupied the left iliac fossa. It extended across the midline, upward as far as the umbilicus, and pushed the bladder, left ureter, and sigmoid colon to the right. The left iliac vessels were embedded in it. A biopsy caused severe bleeding. Radiotherapy was started December 26, and continued at intervals to August 10, 1936. The factors were 200 kv., 25 ma., 50 cm. TSD, filter 1 mm. Cu+1 mm. Al; three fields of 15×15 cm. and 10×15 cm. were used. The total dose was 7300 r measured in air. The tumor shrank but did not disappear. On April 25, 1942, the tumor measured 19.5 cm.

transverscly in the roentgcnogram, and the left leg was somewhat swollen. This increased and became painful. From July 21 to August 26, 1943, he was given more roentgenotherapy, totalling 3000 r in air, through two 15×20 cm. anterior and posterior fields, using the same factors, except that the filter was 2 mm. Cu+Al. A third course, begun April 17, 1944, and ended November 13, 1944, used two anterior, two posterior, and two lateral pelvic fields to give another 6400 r. These again gave some relief, but the tumor continued to grow, causing dilatation to the superficial veins in the inguinal region, evidences of metastases in the skull and femur with pathological fracture, and, death nine years and eleven months after biopsy. (Fig. 16.)

Case 22. (P & S 29076.) Male; age, 55 years. (Dr. A. G. Foord, Pasadena, California. Presented as Case 31 at Tumor Seminar, held at Los Angeles County Hospital, November 21, 1948; A. P. Stout, Moderator.)

Seven years before, a firm mass had been removed from the medial aspect of the right thigh just above the knee. Two years later, a similar mass was removed from the sternal region, and a year later, the distal end of the left clavicle was removed because of tumor involvement. One year ago, a mass 4.5×3.5×2.5 cm., apparently in a lymph node, was removed from the right groin. Five months ago, an extradural mass was removed at the level of the fifth thoracic vertebra, which was partly destroyed. The present mass, 10.5×7.5×5 cm., was removed from the left axilla. It had grown to that size in a few months. All specimens were alike histologically; the present section is from the axillary mass. Dr. Foord reports that six months after the axillary operation, another retroperitoneal tumor of similar appearance was excised from the subphrenic region. (Fig. 17.)

Case 23. (P & S 26303 and 29484.) Colored male; age, 59 years. (V. A. Hospital, New Orleans, La. S-47-142 and A-48-103. Pathologist: Dr. J. Ziskind.)

The patient had had five months of paraumbilical sharp colicky pain. Roentgenograms were equivocal. A segment of the lower ileum was resected; it contained a sharply constricting, encircling, slightly elevated, and deeply ulcerated tumor, 1.7 cm. in width and 4 cm. in thickness. Enlarged mesenteric nodes were also involved. Eighteen months later, the patient died, and autopsy by Dr. Joseph Ziskind showed large metastases in the liver but nowhere else. (Fig. 18.)

Case 24. (P & S 19853 and 20214.) Female, age, 27 years. (Tissue received from Dr. A. O Severance, Nix Hospital, San Antonio, Texas who obtained it from Dr. Paul Brindley Pathologist, and Dr. S. R. Snodgrass, Surgeon University of Texas, Galveston.)

One year before the patient was seen her head had been injured in an automobile accident. A lump appeared and was stationary until two months before, when it began to grow. At operation, there was a subcutaneous mass, which communicated with a deep intracranial mass, through a 3-cm. defect in the skull. Before the operation was completed there was great loss of blood and in spite of transfusions and infusions she went into shock and died. The skull was opened after death, and a 4-cm. tumor was found on the dura; it had extended deeply between the two hemispheres and impinged upon without infiltrating the right hemisphere. The superior sagittal sinus was completely occluded by the tumor. Its total weight was 62 gm. (Fig. 19.)

Case 25. (P & S 19710. Dr. Ellis Kellert, Ellis Hospital, Schenectady, N. Y., and Dr. W. W. Tribby, Methodist Hospital, Memphis, Tenn.) Female purebred collie, 7 years old.

The tumor, 7×3.8 cm., which was from the elbow region, appeared encapsulated and had been present for six to seven months. (Fig. 20.)

Discussion

This study satisfies the writer that the twenty-five tumors in this group and the ten previously reported form a definite clinical and pathological entity. They are basically vascular tumors although their vascular nature cannot always be appreciated clinically or grossly because the capillaries are often occult. Even when the lumina are only potential spaces, these can be detected microscopically, sometimes by their endothelial lining cells and always if their delicate reticulin sheaths are blackened by silver. The tumor cells do not have a fixed size and shape but vary from large to small and from spindle-shaped to rounded. Moreover, connective-tissue fibers are sometimes plentiful between

Cases 1, 5, 12, and 20 are from the Armed Forces Institute of Pathology and are used by permission of Brigadier General Raymond O. Dart, USA, Director.

Cases 2, 9, and 21. The material from these cases comes from the Babies Hospital, New York, and is used with the consent of the pathologist, Dr. Dorothy Anderson.

the cells, and sometimes there are none. Always, however, the tumor cells are packed in solidly to fill the spaces between the capillaries outside of their reticulin sheaths The exact nature of these so-variable cells has not been proved, and Dr. Murray was unable to identify the cellular nature of the only tumor explanted in vitro. However, it seems permissible to suggest that if one can accept the probability of a relationship or linkage between the glomus pericyte, which in ordinary stains is a rather small, rounded cell, on the one hand and the elongated smooth-muscle cell on the other, the various shapes and sizes of the tumor cells in these thirty-five tumors may be explained with some degree of probability This writer at least cannot think of any other reasonable explanation of such a group of vascular tumors He has therefore felt encouraged to continue to use the term "hemangiopericytoma" originally suggested for them.

The tumors are very variable in their behavior and some of them are malignant. In most instances, it does not seem possible to distinguish between the benign and the malignant by the histological appearance. It can be said that none of the congenital cases has proved malignant.

Summary

Twenty-five cases of a rare vascular tumor originally called "hemangiopericytoma" by Stout and Murray are reported in order to display its histological and clinical features.

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FIG. 1. *Case 1. Tumor of neck.* (*Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation.* × 515.)

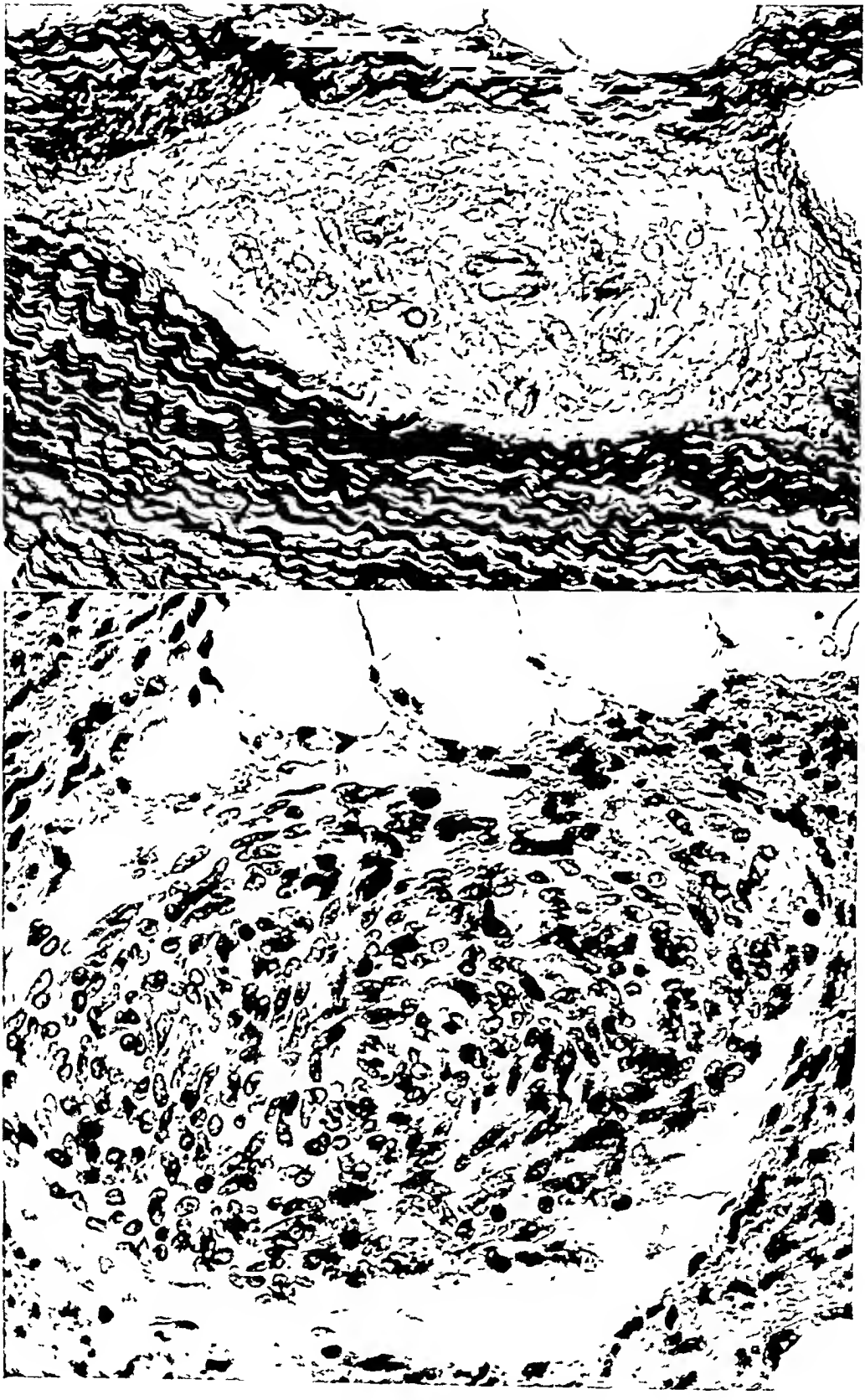

FIG. 2. *Case 2. Tumor of arm. (Left, H & E. stain. Right, Laidlaw silver reticulum impregnation.* × 515)

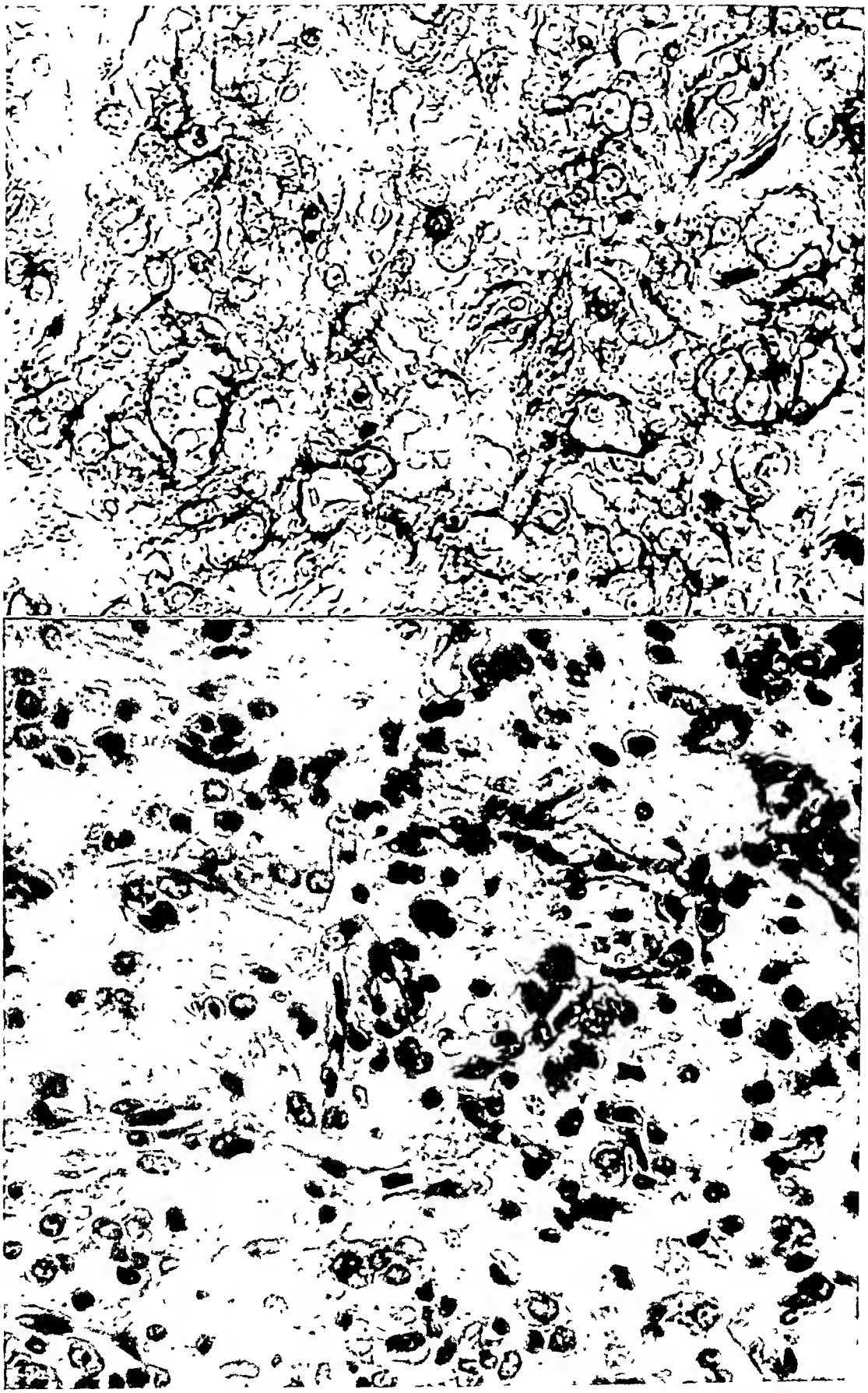

FIG. 3. *Case 3. Tumor of ovarian stroma.*

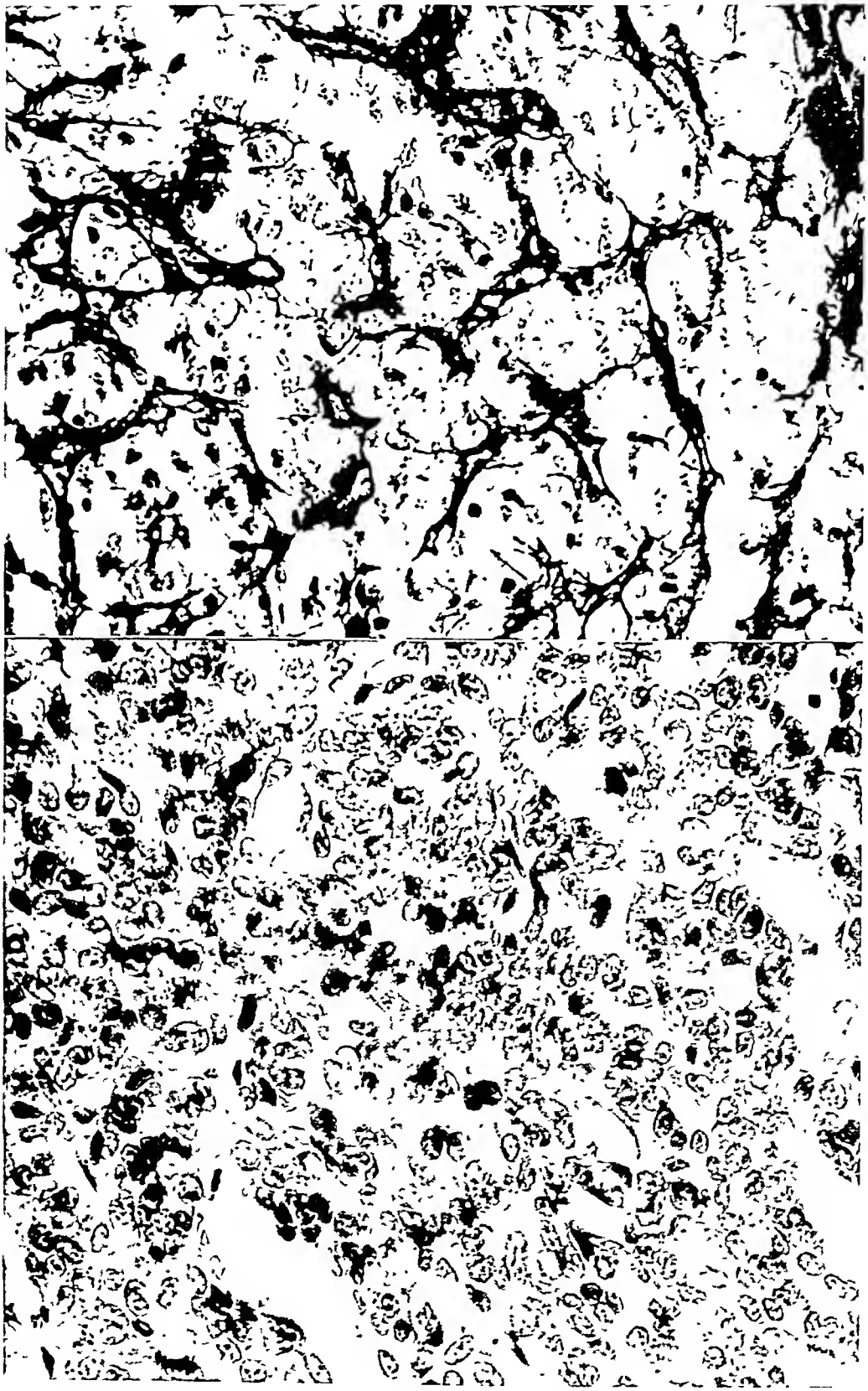

FIG. 4. *Case I. Tumor of tongue. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation. × 515.)*

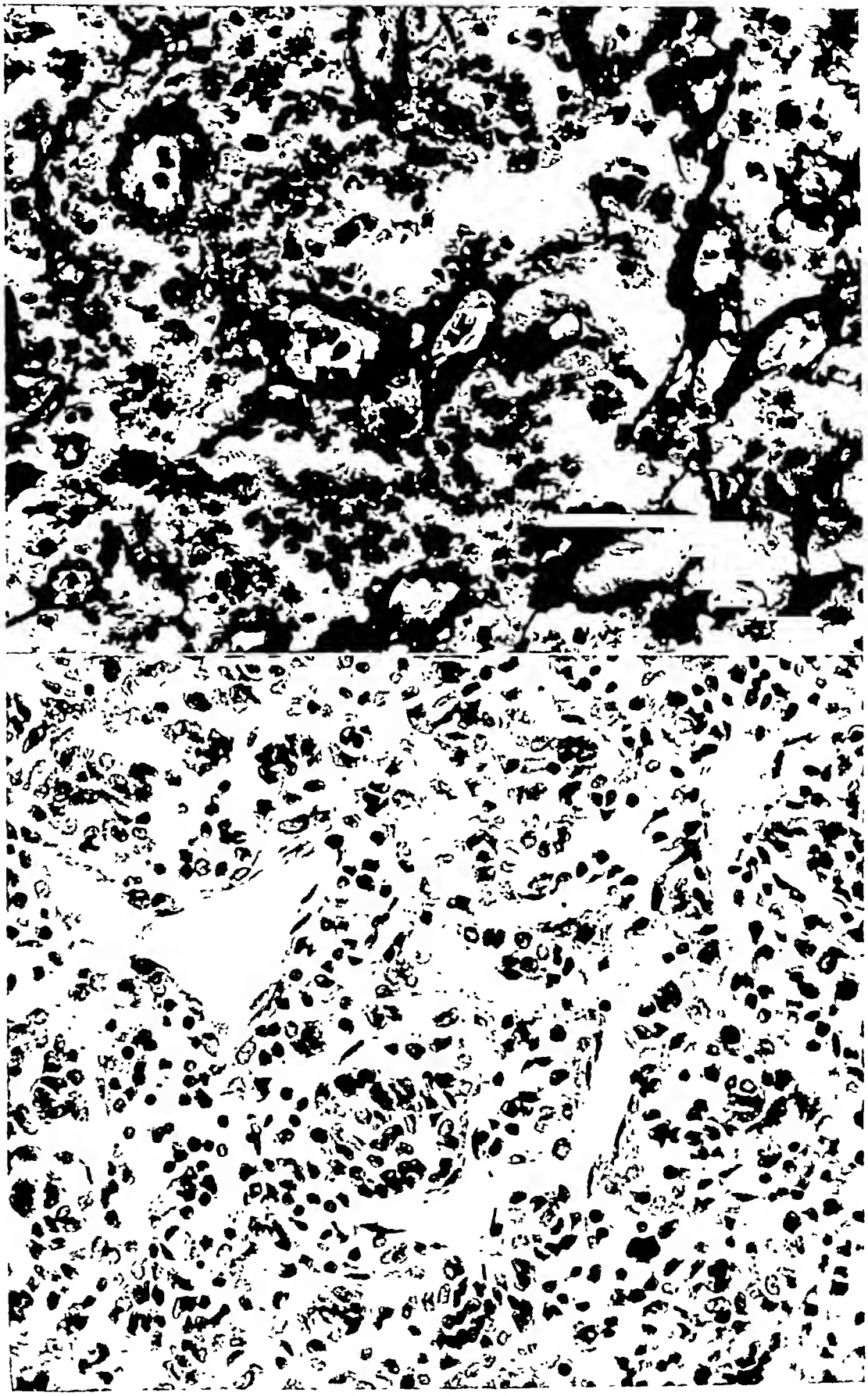

FIG. 5. *Case 6. Tumor of triceps muscle. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation. × 515.)*

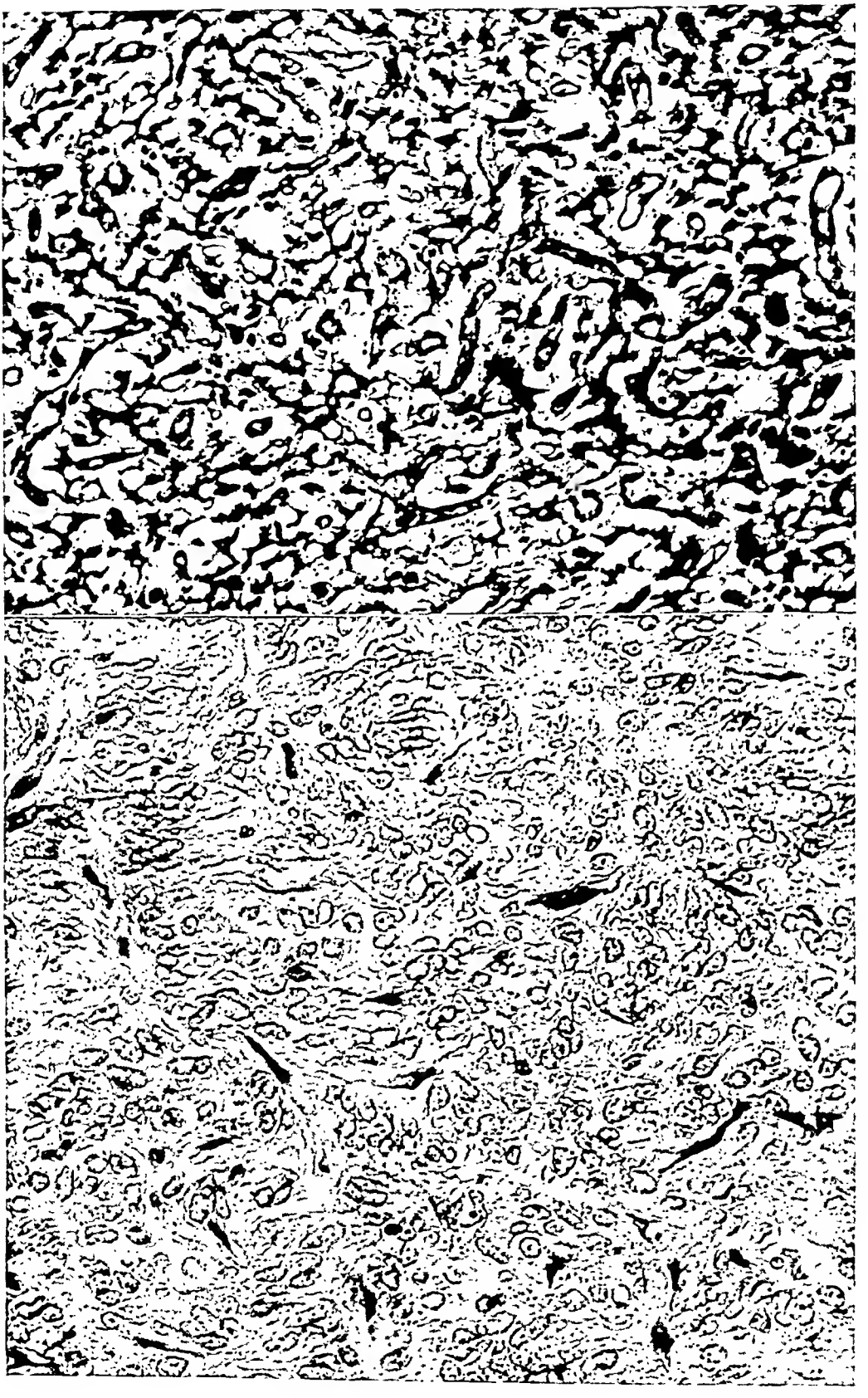

FIG. 6. *Case 7. Tumor of retroperitoneum. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation.* × 515.)

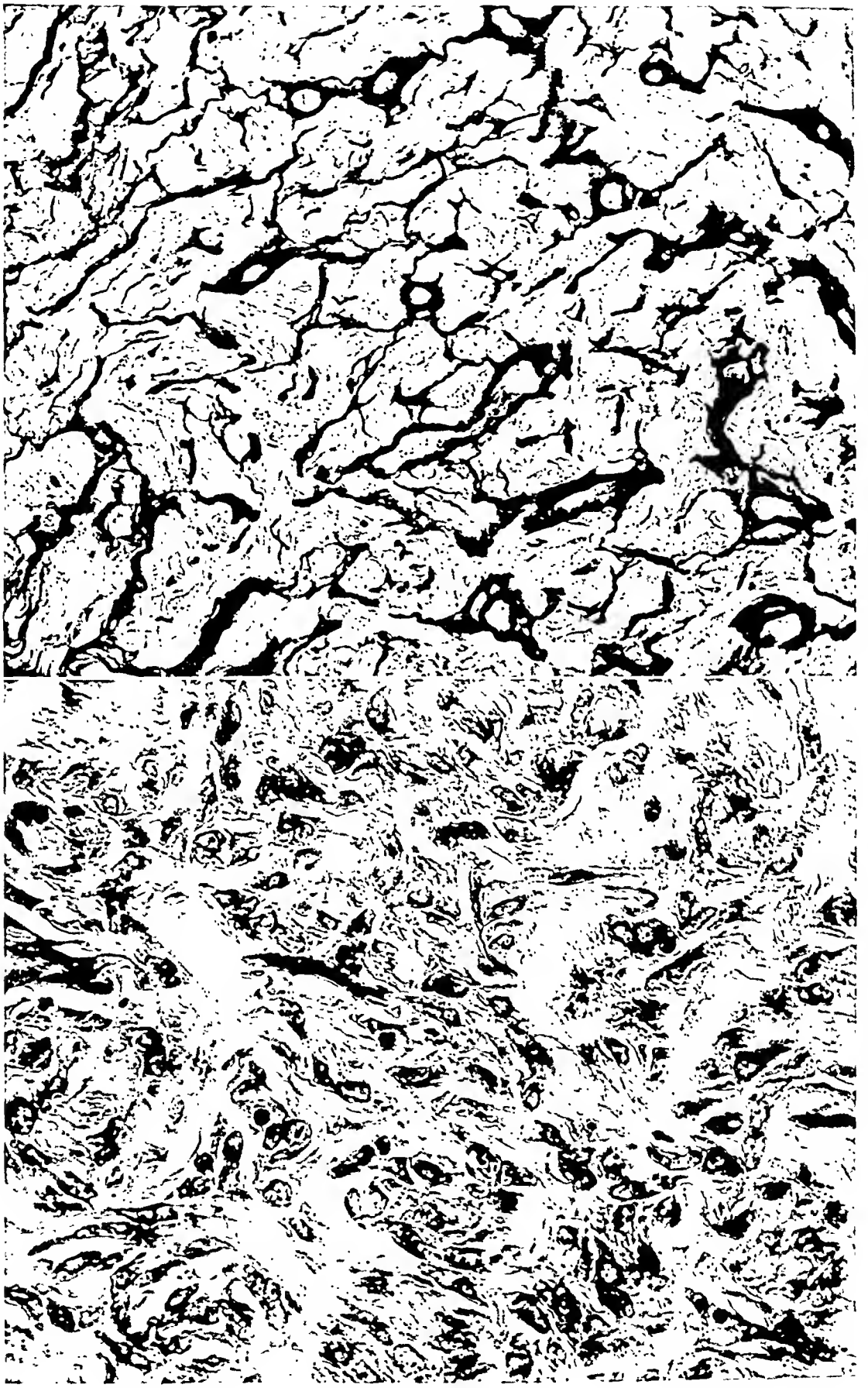

FIG. 7. *Case 8. Tumor of mesentery. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation.* × *515.)*

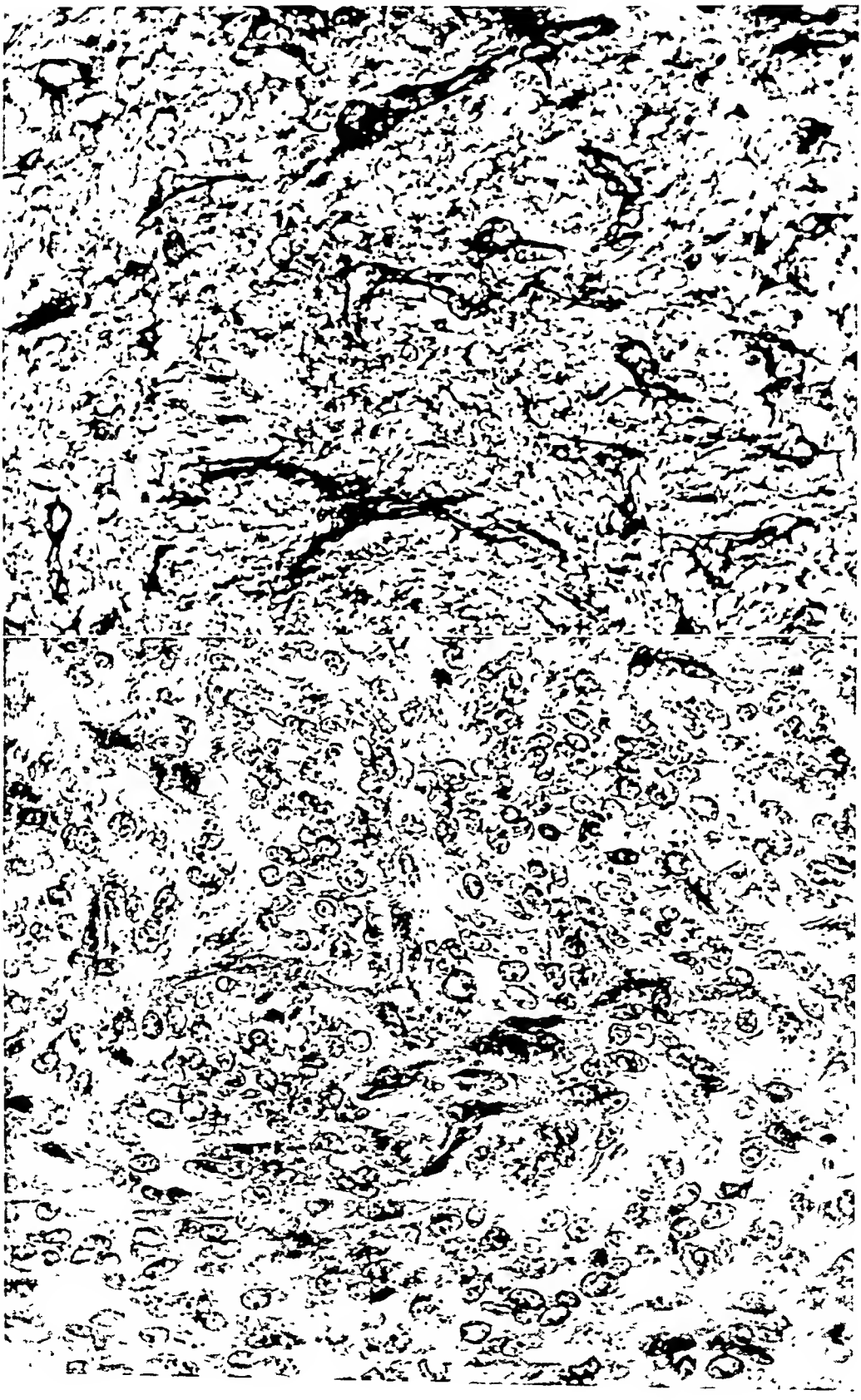

FIG. 8. *Case 9. Tumor of arm. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation. × 515.)*

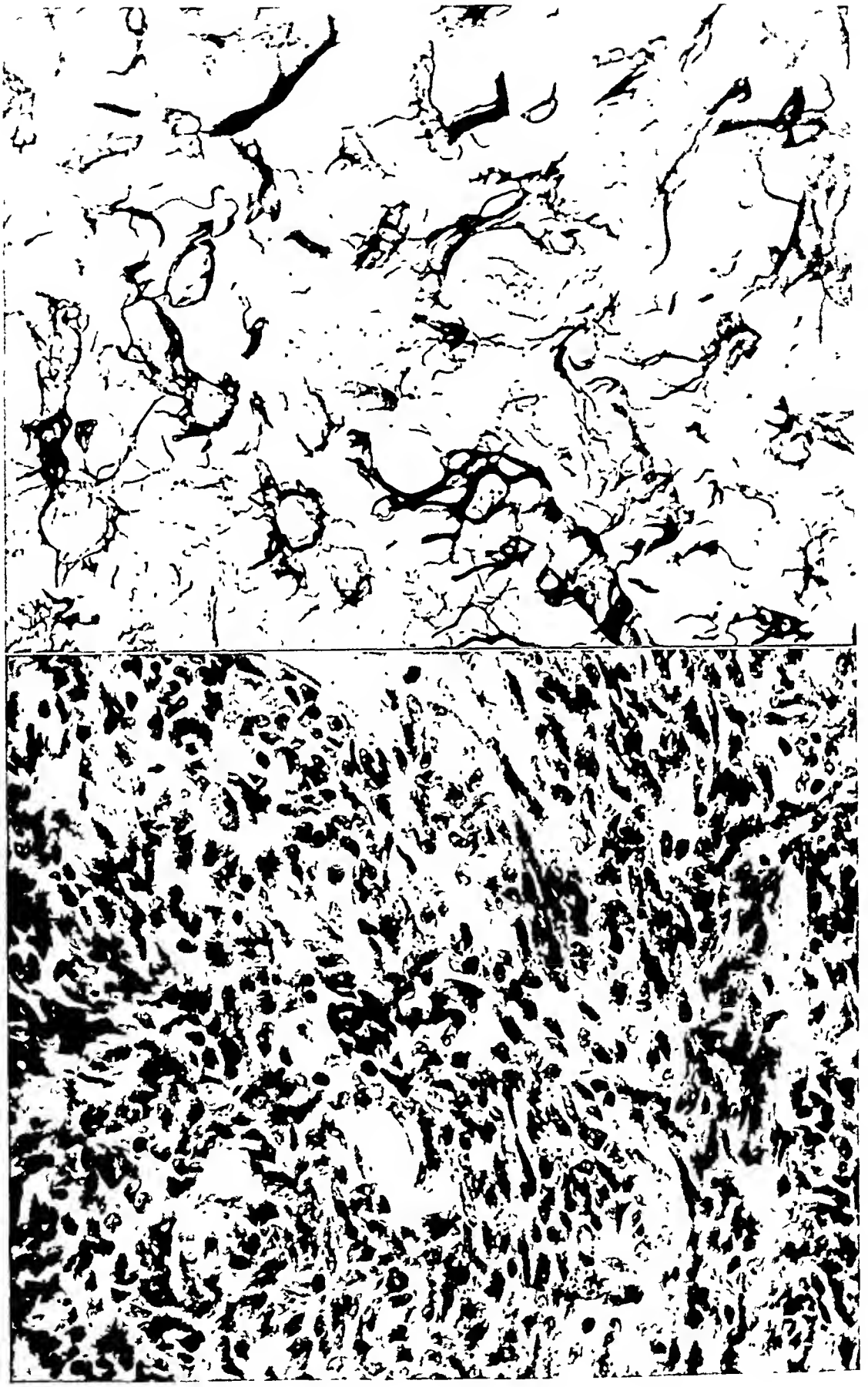

FIG. 9. *Case 10. Tumor of pericardium. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation.* × *515.)*

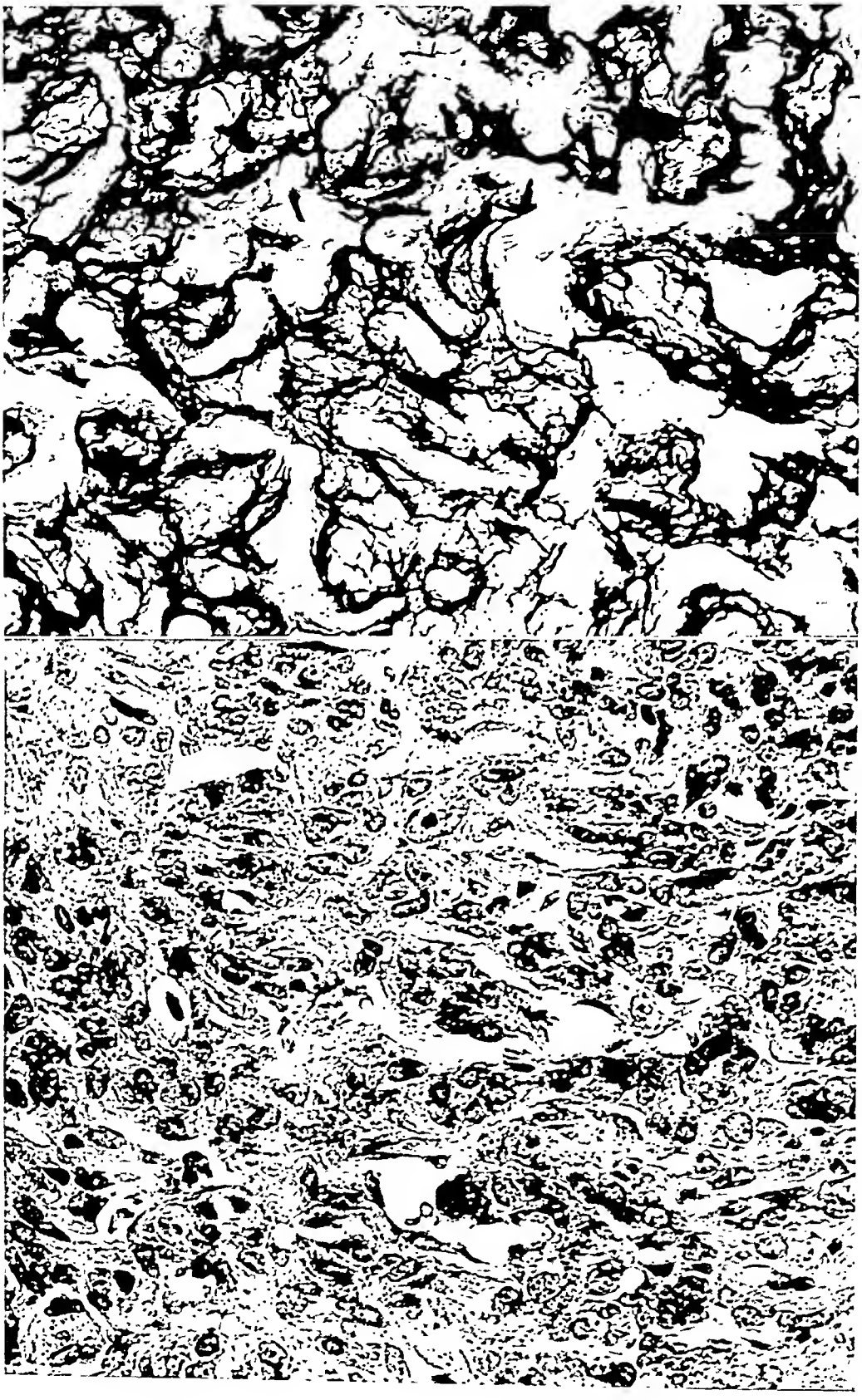

FIG. 10. *Case 11. Tumor of orbit. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation. × 515.)*

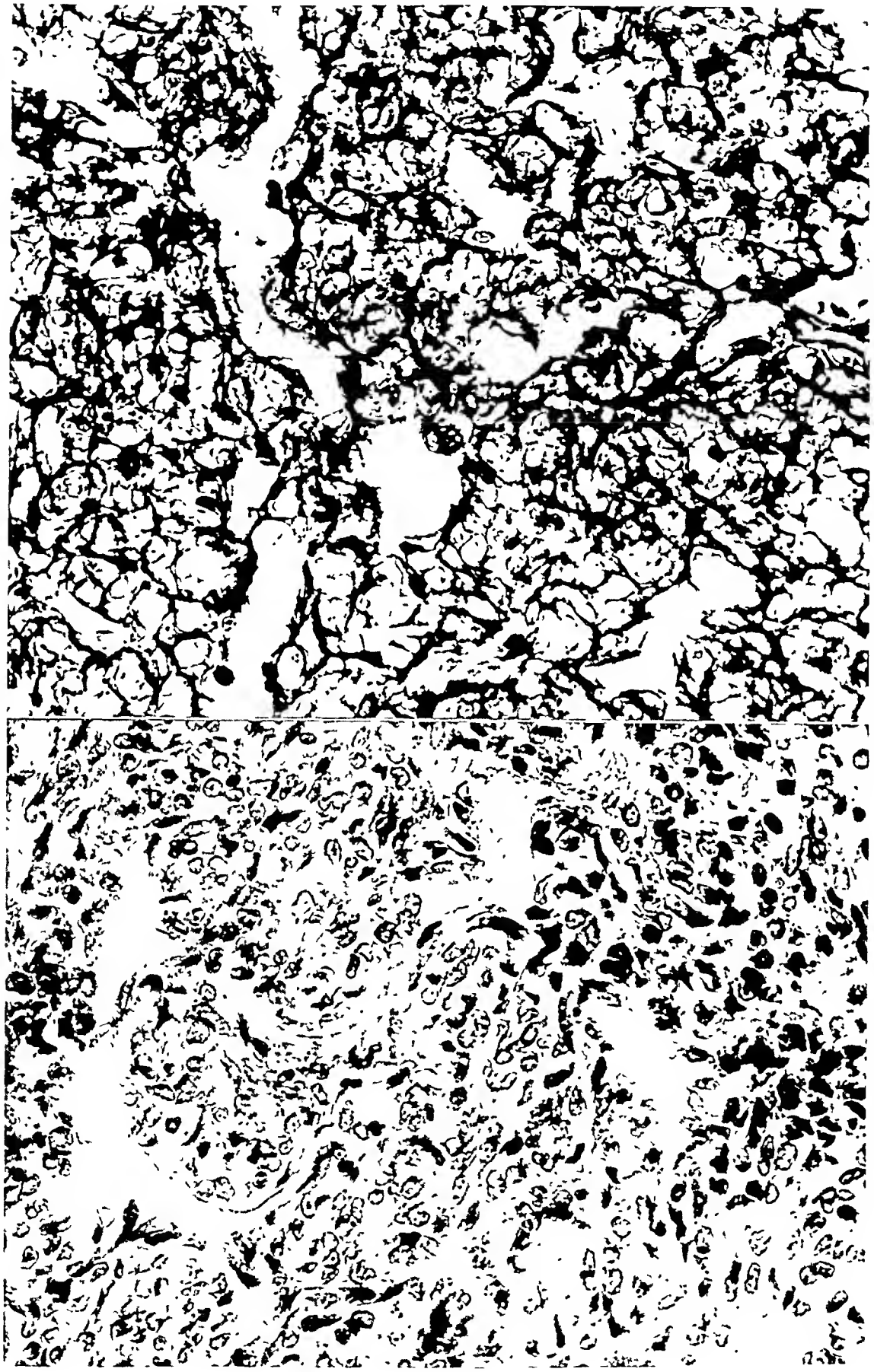

FIG. 11. *Case 12. Tumor cells in alveolar space. Left H. & E. stain. Right, Laidlaw silver reticulin impregnation. × 515.*

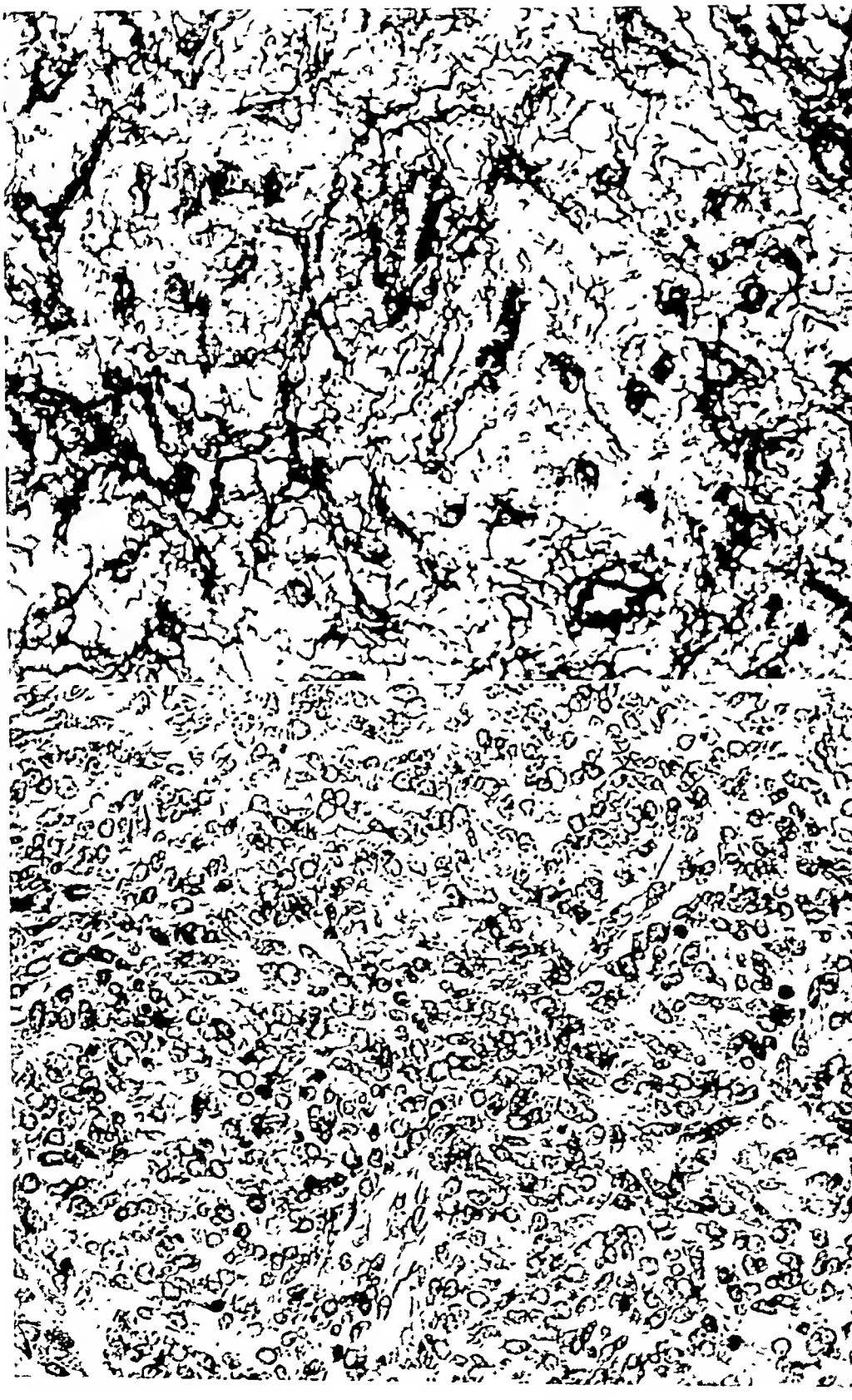

FIG. 12. *Case 13. Tumor of infraorbital region. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation.* × 515).

FIG. 13. *Case 16. Tumor of diaphragm. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation.* × *515.)*

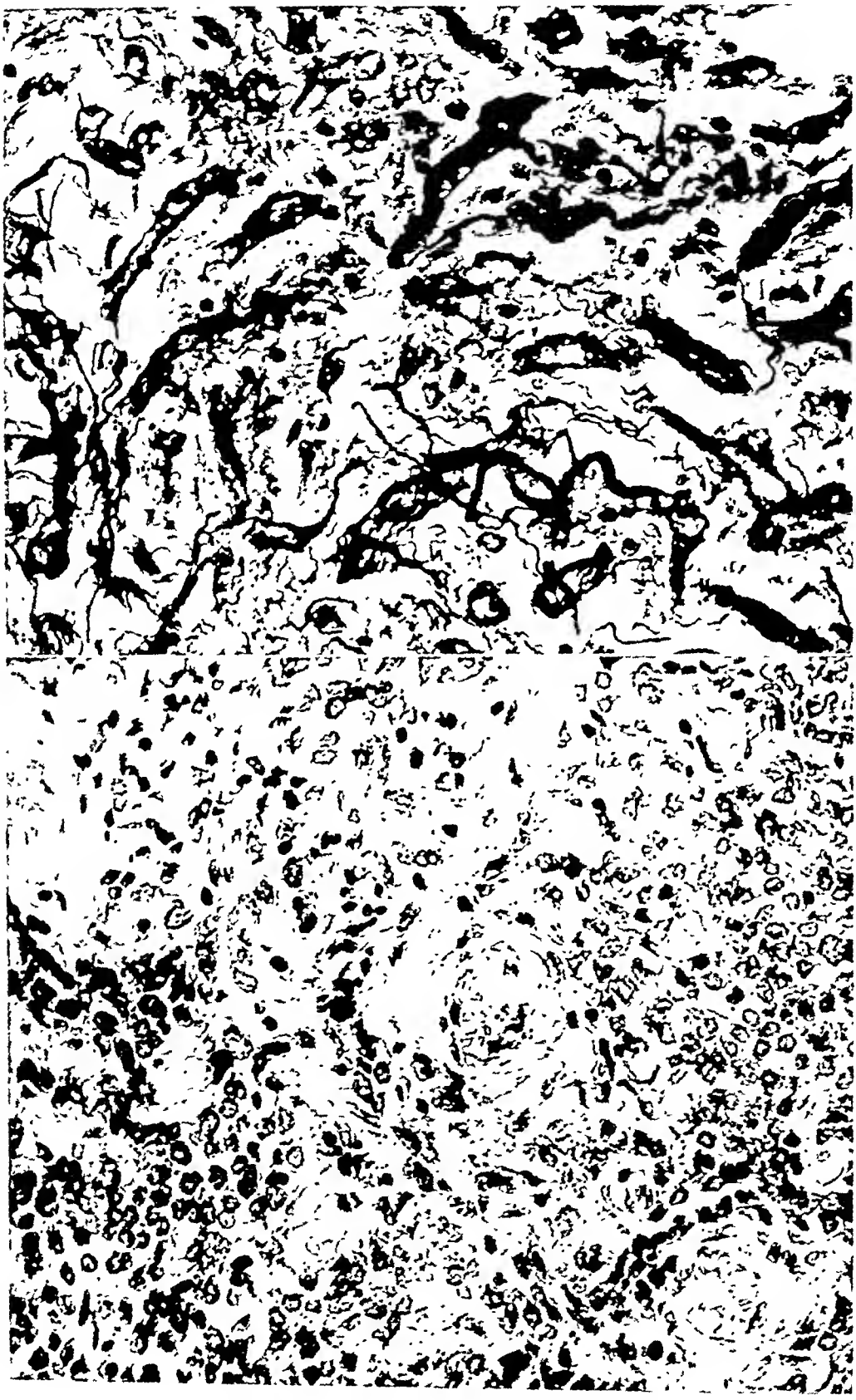

FIG. 14. *Case 18. Tumor of scapular region. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation. × 515.)*

FIG. 15. *Case 20. Tumor of thigh. Left H. & E. stain. Right Lo[illegible] aw silver retic[illegible] impregnatio[illegible] × 515.)*

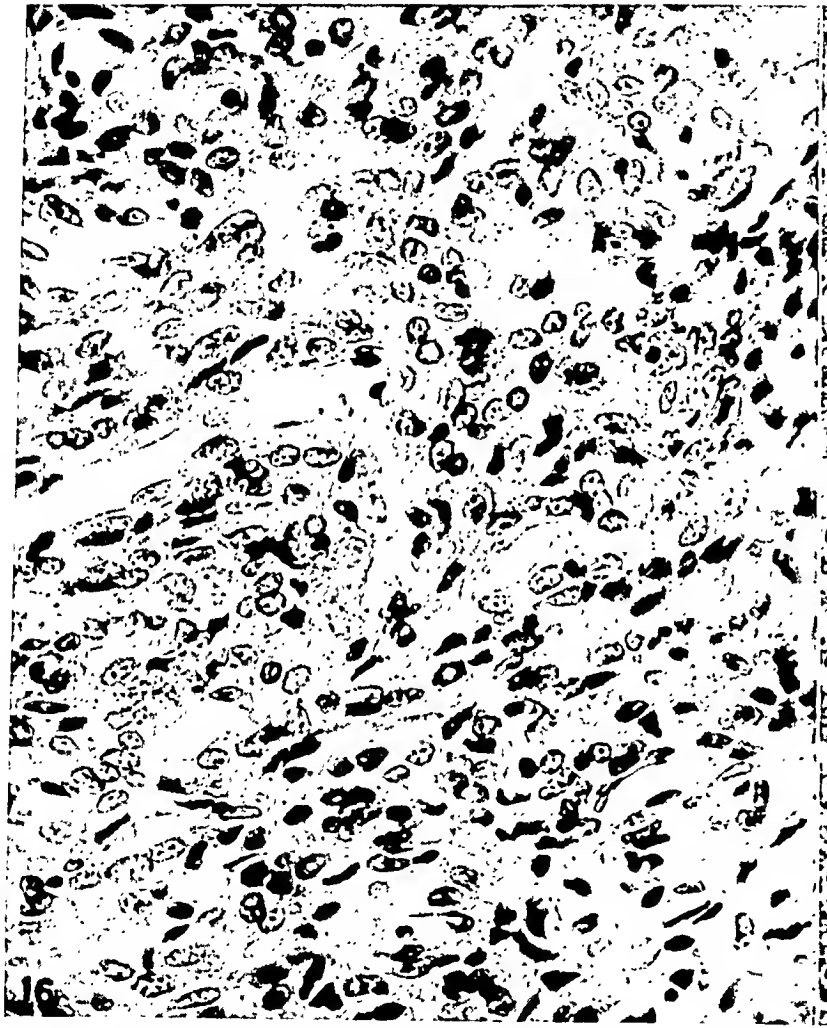

FIG. 16. *Case 21. Tumor of retroperitoneum.* (*H. & E. stain.* × *515.*)

FIG. 17. *Case 22. Tumor of thigh.* (*H. & E. stain.* × *280.*)

FIG. 18. *Case 23. Metastasis in liver from tumor of ileum. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation. × 515.)*

FIG. 19. *Case 24. Tumor of cerebral meninges. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation.* × 515.)

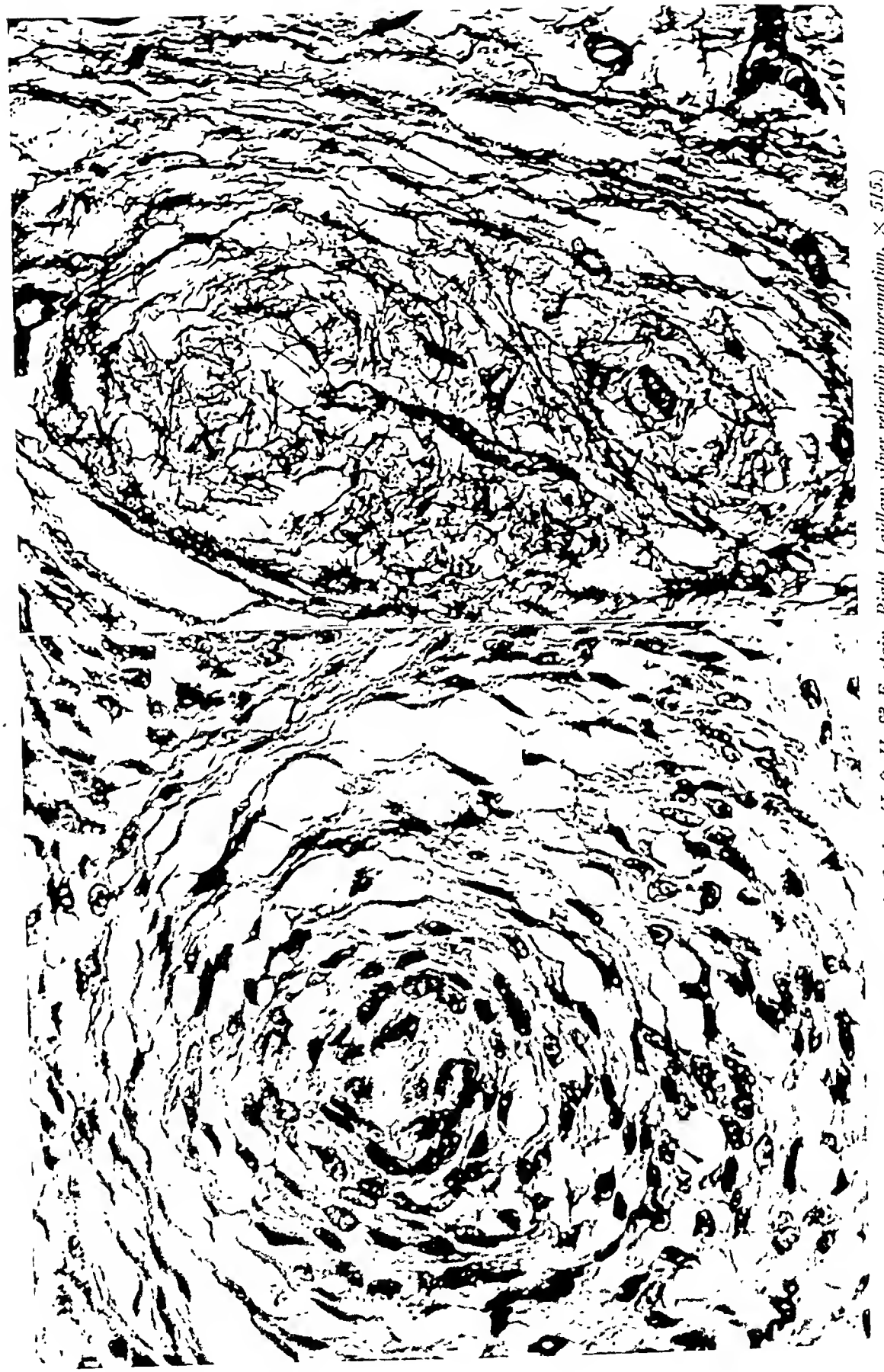

FIG. 20. *Case 25. Tumor of dog's foreleg. (Left, H. & E. stain. Right, Laidlaw silver reticulin impregnation. × 515.)*

SYSTEMIC PATHOLOGICAL EFFECTS OF NITROGEN MUSTARDS, AND A COMPARISON OF TOXICITY, CHEMICAL STRUCTURE, AND CYTOTOXIC EFFECT, WITH REFERENCE TO THE CHEMOTHERAPY OF TUMORS*

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WITH THE TECHNICAL ASSISTANCE OF

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ALTHOUGH compounds of the nitrogen mustard series (substituted 2-chloroethyl amines) have been employed for some time in the treatment of malignant processes in humans, a relatively small number of these compounds (numbers 8, 9, 11, 29, 32, 33 of this series, methyl-bis (2-bromoethyl) amine, and 1, 2, 3, 4 tetrakis [bis (2-chloroethyl) amino] butane) have been reported as used for this purpose.[2, 3, 4, 5, 7, 8, 12]

The present study consists of a report of the visceral lesions observed following intraperitoneal injection, into mice, of a series of nitrogen mustards and related compounds, and of a preliminary attempt to correlate the toxicity, chemical structure, and pathological effects of this series of compounds, with the goal of predicting the potential chemotherapeutic usefulness of nitrogen mustards other than those tried clinically to date.

The conclusions to be reached from the second aspect of this study are based on the assumption that the cytotoxic effect of the nitrogen mustards, which has been found useful in the therapy of malignant processes in man, is related to the cytotoxic effect that these compounds exert on the cells of many normal tissues, particularly those with actively dividing cells.[5] Although this supposition formed the basis for the original chemotherapeutic trials in humans, there is as yet no direct evidence to support its validity. There is equally, however, no direct evidence against it, and, since there are as yet no other criteria that can be used as a basis for predicting the effects of nitrogen mustards on human tumors, it was felt that an analysis of the type just mentioned might be of value in extending the clinical utility of these compounds.

A more detailed description of the toxicologic and chemotherapeutic screening program, from which the data presented in this

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Compounds were obtained from the University of Chicago Toxicity Laboratory, The Sloan-Kettering Institute for Cancer Research, and from the Technical Command, Army Chemical Center, Maryland.

The synthesis of compound 1,2-bis [2-(bis-beta-chloroethyl-amino)ethoxy] ethane and related compounds is to be published in the future by B. Witten, Technical Command, Army Chemical Center, Maryland.

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report were obtained, and more complete data on the toxicity of these and other compounds of the nitrogen-mustard series, are presented elsewhere.[6] The present report covers the pathological effects of thirty-four nitrogen mustards and six chemically related compounds.

Methods

All mustards studied in the screening program mentioned[6] that produced fatalities twenty-four or more hours (called delayed deaths) after intraperitoneal injection into 20-gm. male Carworth Farm mice were studied for pathological effects, as well as a few compounds that produced only acute deaths. A group of four mice of approximately the same weight (18 to 25 gm.) received a single intraperitoneal dose of compound, usually amounting to between one and two median lethal doses (LD_{50}). Soluble compounds were suspended in normal saline, and insoluble compounds in 10 per cent gum arabic, drug and diluent together making 1 per cent of the body weight.[6] Four vehicle-injected mice of the same weight served as controls for each compound. At the anticipated time of death, or when the animals appeared moribund (usually 2 to 3 days after injection), complete blood counts were made and the mice sacrificed. The blood study included white-cell, red-cell, and differential counts, and hemoglobin determination; similar counts on eighty-eight untreated mice were used to establish control levels.

At autopsy, the general condition of the animals, and the gross appearance of the lungs, spleen, gastrointestinal tract, liver, kidneys, endocrine organs, and lymphoid tissues were noted, i.e., changes in size, color, and consistency. The organs were fixed in formalin, embedded in paraffin, and sectioned at 5 microns; routinely microscopic examinations were made of the heart, lungs, spleen, gastrointestinal tract, pancreas, liver, kidneys, adrenal, testis, thymus, lymph nodes, and bone marrow. For certain compounds, additional organs, such as brain, thyroid, and skeletal muscle, were examined.

Results

Gross Pathology

The major gross pathological changes noted were hypotrophy of the spleen, thymus, and lymph nodes, and dilatation of the intestine, the lumen being filled with fluid feces. These changes were observed with the majority of the compounds studied, but were not felt to allow quantitation to the degree permitted by the microscopic pathology. One compound [N-(2-benzimidazolemethyl)-N-benzyl(2-chloroethyl) amine] caused the appearance of large amounts of ascitic fluid and acute inflammation of the retroperitoneal and mesenteric fat. None of the other compounds studied in this program produced a comparable effect, even though the majority can be considered primary irritants.

Microscopic Pathology

The major microscopic lesions produced by the thirty-four nitrogen mustards (2-chloroethyl amines) and six chemically related compounds (called nonmustards) studied pathologically in this program to date were, with minor variations, the previously described effects of these compounds;[4,5,7,8,9,11,12] lymphoid, bone-marrow, testicular, and gastrointestinal lesions were most prominent. In addition, renal and pulmonary lesions were observed relatively commonly, and three compounds caused central-nervous-system damage. Table 1 lists the compounds studied by code number, chemical formula, median lethal dose (± 1 standard error, in terms of mg. per Kg. and moles per Kg. $\times 10^6$), amount injected (in mg. per Kg., and in per cent of the median lethal dose), the number of animals autopsied for each compound, and the time of sacrifice, in hours after injection. Table 2 lists, for each compound studied, the code number, the white count and p value,* the relative and absolute lymphocyte and polymorphonuclear leukocyte counts, and

* p is the probability of getting a decrease in the difference of the experimental mean from the control mean as large as that observed due to chance alone.

the degree of pathological change in the various viscera, the symbols being:

0, not examined;
−, negative;
±, questionably damaged;
+, mild damage;
++, moderate damage;
+++, severe damage;
++++, very severe damage.

Although an effort is made in this report to group these nitrogen mustards in terms of their relative effects on the different organs, it must be borne in mind that the data are not strictly comparable, since exactly identical doses (in terms of the LD_{50} dose) were not used for the various compounds, and, for each compound, the animals were sacrificed just before the expected time of death rather than after a constant period of exposure. As a result, variations in the relative rates of onset and progression of the lesions in the various organs, rather than an absolute presence or absence of ability to produce the lesions, may well account for many of the differences between compounds noted in this study. The data are, however, presented for the information they may furnish toward a correlation of chemical structure and properties with toxic effect for this group of compounds, inasmuch as they represent the effects

TABLE 1

NITROGEN MUSTARDS AND RELATED COMPOUNDS COVERED IN THIS REPORT*

Comp † no	Chemical formula	LD_{50} ±1 Stand. error		Amt Injected		No. of animals autop	Time sacrifice (hrs)
		Mg/Kg.	Moles/Kg × 10^6	Mg./Kg	Ratio to LD_{50}		
1	2-Chloroethyl morpholine	161 ±6	865 ±31	150 0	0.93	6	48
2	Ethyl (2-chloroethyl) (3-chloropropyl) amine	24 8 ±1 4	112 ±6	50 0	2 02	4	48
3	Propane, 1-phenyl-1-chloro-2[methyl (2-chloroethyl) amine]	19.9 ±3.0	70 4 ±10 6	32 0	1.61	6	24
4	N-(2-benzimidazolemethyl)-N-benzyl (2-chloroethyl) amine	121 9	326 ±26	125 0	1 03	4	48
5	Dibenzyl (2-chloroethyl) amine	149 ±20	503 ±67	300 0	2 01	3	24
6	Diethyl (4-chloropentenyl) amine	102 ±7	476 ±33	80 0	0 79	4	96
7	Ethyl (2-chloroethyl) amine	1120 ±65	7790 ±448	1100	0 98	5	72
8	Dimethyl (2-chloroethyl) amine	280 ±14	1950 ±100	272 2	0.97	5	72
9	Methyl-bis (2-chloroethyl) amine	4 13 ±0.37	21.5 ±1 9	8 40	2 03	4	48
10	s-Propyl-bis (2-chloroethyl) amine	1.33 ±0 12	6 02 ±0.55	2 66	2 0	5	72
11	Ethyl-bis (2-chloroethyl) amine	1.56 ±0 05	7.54 ±0 22	3 50	2 25	4	48
12	2-Methoxyethyl-bis (2-chloroethyl) amine	2 41 ±0 39	10 2 ±1 6	5 0	2 08	4	2-72 2-96
13	Tetrahydrofurfuryl-bis (2-chloroethyl) amine	4 96 ±1 15	18 9 ±4 4	10 80	2 18	4	48
14	Methyl-bis (2-chloroethyl-mercaptoethyl) amine	7 58 ±0 22	24 2 ±0 7	14 60	1 93	4	72
15	2-Chloroallyl-bis (2-chloroethyl) amine	19.3 ±1 6	76 2 ±6 2	44 0	2.28	4	48
16	Furfuryl-bis (2-chloroethyl) amine	11 8 ±0 6	45 6 ±2 3	18 80	1.59	4	48
17	n-Propyl-bis (2-chloroethyl) amine	1 35 ±0 12	6 13 ±0 54	2 70	2 0	4	48
18	Bis (2-chloroethyl) amine	168 ±10	940 ±55	404 0	2 41	4	24
19	Allyl-bis (2-chloroethyl) amine	3 32 ±0 34	15 2 ±1 6	4 80	1 44	8	2-72 3-96
20	n-Butyl-bis (2-chloroethyl) amine	4 89 ±0 67	20 8 ±2 9	11 60	2 37	2	48
21	sec. Butyl-bis (2-chloroethyl) amine	2 80 ±0 46	11 9 ±1 9	5 80	2 07	4	48
22	s-Butyl-bis (2-chloroethyl) amine	4.42 ±0 34	18 9 ±1 4	10 8	2 44	3	48
23	tert. Butyl-bis (2-chloroethyl) amine	1 42 ±0 08	6 04 ±0 33	2 50	1 76	6	4 24 2-72
24	Benzyl-bis (2-chloroethyl) amine	28 2 ±4 6	105 ±17	59 40	2 11	5	48
25	2-Acetylethyl-bis (2-chloroethyl) amine	4 69 ±0 62	15 5 ±2.1	7 80	1 66	4	72
26	Phenyl-bis (2-chloroethyl-mercaptoethyl) amine	691 ±50	1840 ±132	900	1 30	4	48
27	3-Chlorobutyl-bis (2-chloroethyl) amine	8 13 ±0 81	30 2 ±3 0	16 0	1 97	4	72
28	o-Nitrophenyl-thio-bis (2-chloroethyl) amine	>5000	>17 000	1000	<0 2	4	72
29	Tris (2-chloroethyl) amine	2 02 ±0 26	8 37 ±1 08	3 76	1.87	4	72
30	N, N, N′, N′-tetrakis (2-chloroethyl) ethylene diamine	16 4 ±0.5	42 9 ±1 4	35 40	2 15	4	48
31	Bis [2-bis (2-chloroethyl) amino-ethyl] sulfide	6 95 ±0 72	14 9 ±1 6	12 0	1 73	6	48
32	N, N, N′, N′-tetrakis (2-chloroethyl) propylene-1,3-diamine	3 64 ±0 44	9 50 ±1 55	5 4	1.48	4	72
33	N, N, N′, N′-tetrakis (2-chloroethyl)-2-chloro-propylene-1 3 diamine	31 7 ±1 0	71 4 ±2.3	33 4	1 05	4	48
34	1,2-Bis [2-(bis (2-chloroethyl) amino) ethoxy] ethane	4 11 ±1 18	8 72 ±2 50	20 0	4 87	4	48
35	Dimethyl-bis (2-chloroethyl) ammonium chloride	67 0 ±2 9	324 ±14	75 0	1 12	4	48
36	1,4-Di (2-chloroethyl)-1,4-diethyl piperazinium dichloride	795 ±140	2340 ±412	700 0	0 88	4	72
37	Methyl-bis [2-(methyl-bis (2-hydroxyethyl) ammonium chloride) ethyl] amine	463 ±7 1	1170 ±18	475	1 03	4	24
38	Morpholine	413 ±26	4740 ±293	350	0 85	4	72
39	2-Hydroxyethyl morpholine	3600 ±1050	23,600 ±6860	2500	0 69	4	24
40	Tris (2-hydroxyethyl) amine	>5000	>26,900	1250	<0 25	4	48

* The nitrogen mustards used were in the form of the hydrochloride salt, with the exception of compound 25, which was a hydrobromide hemihydrate

† The compound numbers are not to be construed as official code numbers The compounds are given these numbers by the author merely for purposes of cross reference

TABLE 2

EFFECTS OF NITROGEN MUSTARDS AND RELATED COMPOUNDS ON PERIPHERAL BLOOD AND VISCERA

Comp. no.	Average white count	p	% Polymorphonucleors	% Lymphocytes	Absolute polymorphonucleor count	Absolute lymphocyte count	Lymphoid tissues: Spleen	Thymus	Lymph nodes	Bone morrow	Lungs	Gastrointestinal tract: Kidneys	Mucus changes	Cell changes	Ulcers	Testes	Others
1	4360 ± 739	0.004	47.5	48.3	2071	2106	+	+	−	0	+	++	+	−	−	++	Brain++
2	3625 ± 105	0.005	24.0	75.0	870	2719	+	+	0	0	−	+	−	−	−	+	
3	7650 ± 1375	0.065	49.3	50.3	3749	3823	+++	+++	+++	+	±	+	−	±	−	+	
4	9362 ± 1566	0.16	16.5	81.5	1565	7630	±	−	0	0	−	−	−	−	−	−	{Ascites
5	3150 ± 725	0.011	31.0	68.7	977	2164	+	+	+	±	+	+	−	−	−	+	{Retroperitonitis
6	14,950 ± 3749	not sig.	10.5	88.8	1570	13,231	±	0	−	−	+	±	−	−	−	+	
7	32,500 ± 10,051	not sig.	18.8	81.0	6110	26,325	±	±	−	−	−	+	−	−	−	−	
8	11,810 ± 1565	not sig.	25.2	74.8	2976	8834	±	−	0	−	0	±	+	−	−	±	Brain++
9	3700 ± 1319	0.0045	49.8	50.2	1843	1927	+	+	+	+	+	+	+	+	−	++	
10	6410 ± 1096	0.019	17.8	81.4	1141	5218	−	−	−	−	−	+	−	±	−	++	
11	5475 ± 1882	0.0225	28.5	70.8	1560	3876	+	0	+	±	±	±	−	++	−	+	
12	3200 ± 842	0.00175	13.0	86.0	416	2752	±	0	0	+	−	±	+	+	++	+	
13	1681 ± 288	0.00125	17.5	82.5	224	1387	++	0	+++	+++	+	±	−	+	++	+	
14	3670 ± 1378	0.00225	10.0	89.0	367	3206	±	++	−	++	±	±	−	±	−	±	
15	675 ± 179	0.00045	0.0	100.0	0	675	++	+++	++	+++	+	±	−	+	−	++	
16	3975 ± 511	0.0065	57.5	41.5	2285.6	1649.6	+	0	0	+++	−	±	−	+	−	+	
17	7787 ± 569	0.07	46.3	53.0	3605	4127	+	+++	+	−	±	−	−	−	−	±	
18	8050 ± 2792	0.085	88.2	11.5	7100	925	+++	0	+++	++	+	+	±	+	−	++	
19	4180 ± 351	0.0035	37.2	60.4	1555	2525	±	0	0	−	+	+	−	±	−	+	
20	3875 ± 1254	0.006	11.0	88.5	426	3429	+	0	++	+++	±	−	−	−	−	±	
21	6387 ± 1618	0.03	48.8	50.0	3117	3194	+	0	+	±	−	+	±	+	−	0	
22	5483 ± 1484	0.035	36.0	62.7	1974	3438	+	+	±	+	±	+	−	−	−	++	
23	5087 ± 924	0.014	15.3	84.5	878	4299	++	0	0	−	−	+	±	−	−	+	
24	3100 ± 799	0.0035	79.0	21.0	2449	651	++	0	++	+++	−	−	−	−	−	+	
25	5987 ± 1210	0.024	36.0	62.5	2155	3733	+	+	+	−	±	−	−	±	−	+	
26	5950 ± 1494	0.023	62.3	37.3	3707	2219	++	++	++	++	±	±	−	±	−	+	
27	3375 ± 868	0.0045	19.8	79.3	668	2676	−	+	−	++	−	±	−	±	−	++	
28	15,500 ± 1924	not sig.	15.5	84.0	2303	13,020	−	0	0	−	−	−	−	−	−	−	
29	1167 ± 508	0.0025	16.7	81.7	195	953	++	++	++	++	−	±	−	±	−	++	
30	1961 ± 841	0.00045	38.0	62.0	745	1216	+++	0	++	+++	±	+	−	+	−	++	
31	4567 ± 895	0.0225	89.0	11.0	4065	492	++	+	+	+	−	+	+	−	−	+	
32	1700 ± 305	0.00035	9.8	87.8	167	1664	±	−	0	+	−	−	+	−	−	+	
33	5062 ± 456	0.0135	47.3	52.0	2394	2632	++	0	+	+	−	+	+	+	++	+	
34	3633 ± 477	0.0009	92.2	7.2	3350	262	++++	++++	+++	+++	−	−	±	±	−	−	
35	10.037 ± 1011	0.185	12.0	87.0	1204	8722	−	0	+	−	−	±	±	−	−	+	
36	21,087 ± 2934	not sig.	7.3	92.2	1539	18,463	−	0	−	−	±	±	+	−	−	±	
37	15,112 ± 674	not sig.	7.3	91.5	1103	13,828	−	0	−	−	−	−	±	−	−	−	
38	14,880 ± 4230	not sig.	18.0	80.8	2678	12,023	±	0	−	−	−	±	−	−	−	+	
39	12,790 ± 2300	not sig.	23.5	73.5	3006	9381	−	0	0	−	±	±	−	−	−	±	
40	16,680 ± 2391	not sig.	14.0	85.6	2335	14,278	+	±	−	−	0	−	−	−	−	±	
Controls	13,400 ± 790		17.0	81.1	2278	10,867											

found at more or less comparable stages of intoxication.

Peripheral Blood. As already indicated, the following studies were done immediately before sacrifice on the peripheral blood of the animals to be autopsied: white-cell count; differential white-cell count; red-cell count; hemoglobin determination.

The averaged determinations for each compound, with standard error where possible, and control values with standard error, are given in Table 2. Depression of the total white count, one of the most consistent effects of the mustards[5, 7] was further analyzed statistically by the determination of p values. Compounds 12, 13, 14, 15, 29, 30, 32, and 34 produced a significant effect on the white count ($p<0.0027$); 1, 2, 5, 9, 10, 11, 16, 19, 20, 21, 22, 23, 24, 25, 26, 27, 31, and 33, a probably significant one ($p=0.0027$—0.046); and 3, 4, 6, 7, 8, 17, 18, 28, 35, 36, 37, 38, 39, and 40, a not significant one ($p>0.046$) (see Table 1).

As can be seen, there is a general tendency for more active compounds, in terms both of relatively low LD_{50}'s and ability to produce visceral damage, to produce relatively low peripheral-blood white counts. The correlation is not extremely sharp, however, probably for the following reason. The characteristic behavior of the circulating leukocytes after a lethal dose of a mustard is given parenterally to a mouse is shown in Fig. 1.[13]

Thus, the point on this curve at which the counts are taken determines the white count, and the absolute and relative lymphocyte and polymorphonuclear leukocyte counts; although the pattern of this curve is probably essentially the same for all significantly toxic mustards, the exact time relations are not the same for all compounds, so that precise correlations cannot be made from the results of a study of this type. In addition, the point on the curve at which the blood counts are taken (i.e., immediately antemortem) depends not only on the mustard effect of the various compounds, but also on the nature and severity of side actions on the central nervous system and other organs.

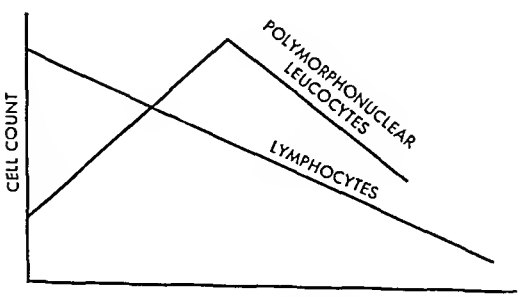

FIG. 1. *Scheme of behavior of peripheral-blood white cells following injection of a nitrogen mustard.*

In general, the more active compounds produced low relative and absolute lymphocyte counts in addition to the low white count; no significant tendency for the absolute polymorphonuclear count to fall under the conditions of this study was noted, so that the relative polymorphonuclear count tended to rise when systemic damage was more marked. No significant changes in monocyte, eosinophile, and basophile counts could be demonstrated, nor did the red-cell count and the hemoglobin level show significant changes with any drug. The white-cell changes in the peripheral blood are compared specifically with the changes in the lymphoid tissues and bone marrow in the following two sections.

Lymphoid Tissues (Spleen, Thymus, Lymph Nodes). As Table 2 shows, there was a general tendency for these nitrogen mustards to produce the same degree of damage to the various components of the lymphoid system. As a result, the following discussion treats this system as a unit, rather than considering the various components separately.

The earliest change noted was usually hypocellularity of the red pulp of the spleen; with more severe damage, the lymphoid follicles of the spleen, thymic cortex, and lymph nodes (retroperitoneal and mesenteric nodes were those studied), showed pyknosis and fragmentation of lymphocytes. The lymphoid tissues from animals with lesser degrees of damage showed reticulum-cell proliferation and phagocytosis of cell debris, the picture somewhat resembling the "toxic reaction" of acute infections, but in those from animals with more severe degrees of damage, the

lesions progressed to extreme hypocellularity without the appearance of phagocytosis of debris—probably by complete cell lysis. When the damage was moderate or severe, the spleen, thymus, and nodes, were smaller than normal. (The hypocellularity of the spleen in severe nitrogen-mustard damage may resemble somewhat the hypocellularity and pseudofibrosis seen in old age in rodents,[1] and this must be borne in mind in studies that do not use young adult animals.) The effects of these compounds on the lymphoid cells of the peripheral blood have been discussed.

As is shown in Table 2, the lymphoid system was, in general, somewhat more sensitive to these compounds than the bone marrow, indicating that the lesser degrees of lymphoid damage described here as suggesting "toxic reaction" represent a nonspecific response rather than a true mustard effect.

With increasing severity of damage to the lymphoid system, the total white count, the absolute lymphocyte count, and the relative lymphocyte count all tended to fall. The absolute polymorphonuclear leukocyte count showed no significant change, and the relative polymorphonuclear count thus tended to rise. Further, there was some, although not a very marked, tendency for compounds with a lower LD_{50} to have a more pronounced effect on both the peripheral blood lymphocytes and the lymphoid tissues; thus, all compounds producing effects graded ++ or more have an LD_{50} (in moles per Kg. $\times 10^6$) less than 1000, except phenyl-bis (2-chloroethyl-mercaptoethyl) amine. Similarly all six nonmustards studied, and all the mono 2-chloroethyl compounds studied except propane, 1-phenyl-1-chloro-2[methyl (2-chloroethyl) amine], produced lymphoid-system damage graded + or less.

Bone Marrow. Table 2 lists the effect of these compounds on the bone marrow. The mildest change observed consisted of pyknosis of many nuclei and cosinophilia of the cytoplasm of many cells; intermediate stages of damage showed hypocellularity that progressed rapidly in the more severe cases to advanced damage, consisting of extreme hypocellularity and congestion of the marrow, the intercapillary spaces being filled with pale protein coagulum, red cells, and small amounts of cell debris. Phagocytosis of cell debris by macrophages was rare, and the mechanism of the hypocellularity appears to be largely direct cell lysis, although the extent of release of cells to the blood stream, with later lysis or destruction, cannot be estimated. Sternal marrow was the source usually studied, but femur, hyoid, and tail-vertebra marrows were also examined in a number of instances; no difference in response in the various bones was noted, nor did the bone marrow appear to differ significantly in susceptibility to these compounds from the myelopoietic tissue of the red pulp of the spleen. The effects of these compounds on the myeloid cells of the peripheral blood have been discussed.

Examination of Table 2 shows that all six nonmustards produced no recognizable bone-marrow effect, and none of the mono 2-chloroethyl compounds studied produced significant bone-marrow damage except propane, 1-phenyl-1-chloro-2[methyl (2-chloroethyl) amine], which also damaged the lymphoid system more than might be expected from its chemical structure. Under the conditions of this study, no significant change in absolute polymorphonuclear count was associated with increasing severity of bone-marrow damage. However, with this increasing bone-marrow damage the total white count and the absolute lymphocyte count tended to fall, so that the relative polymorphonuclear count tended to rise and the relative lymphocyte count to fall. Surprisingly, all the mustards with very low LD_{50}'s (LD_{50} of 8 moles per Kg. $\times 10^6$ or less) produced insignificant or no bone-marrow damage, a phenomenon that was not observed with the lymphoid system. This phenomenon may be related to the severity of side effects, as already discussed, these compounds being too toxic in the doses given to allow survival adequate for the development of the rather slow bone-marrow degenerative process, or it may indicate that a certain minimum amount of drug is necessary. As a result of this, however, the most marked effects on the bone marrow tend to be

produced by compounds of intermediate toxicity (LD_{50} of 10 to 1000 moles per Kg. $\times 10^6$). LD_{50} values of this order of magnitude thus may represent the range of practicable bone-marrow damage by nitrogen mustards, other effects being equal and survival times being adequate. Obviously, however, the mustard (2-chloroethyl amine) structure is fundamental to the production of this lesion and may actually be the only essential for its production.

Lungs. The most common pulmonary change noted was pyknosis of the cells of the alveolar septa; this occurred with eight compounds (Nos. 1, 5, 6, 9, 13, 15, 18, 19) and was questionably present with a number of others.

All these compounds are nitrogen mustards, and all are relatively toxic (LD_{50} less than 1000 in moles per Kg. $\times 10^6$); however, no closer correlation between chemical structure and this effect can be made than that no compound with more than two 2-chloroethyl groups was observed to produce it—namely, it may be restricted to nitrogen mustards of relatively low molecular weight. Data on the volatility of these compounds, to allow an attempt to correlate this finding with vapor pressures of the compounds, are not available. There is no close correlation between ability to produce this pulmonary change, and ability to produce the other pathological effects of the mustards, nor is there any correlation between the occurrence of this lesion and the time after injection at which the animals were sacrificed. Further, this pulmonary effect is not felt to represent a cytotoxic effect in the sense used earlier, and probably will not correlate with any data obtained in the future on the relative effects of these compounds on tumors.

Two animals in the entire series showed pulmonary edema of significant degree, presumed to be a terminal cardiovascular phenomenon rather than a true mustard effect; pneumonia was never observed, even after relatively long exposures to compounds with marked leukocytotoxic effects.

Kidney. The most frequent renal lesion, seen after compounds 1, 2, 3, 5, 7, 9, 18, 21, 22, 23, 30, 31, and 33, was proximal tubular degeneration, with sloughing of tubular epithelial cytoplasmic protein to form protein coagula in the lumina. No lesions severe enough to produce necrosis or inflammatory response were found nor were the glomeruli observed to be affected. One compound, 2-chloroethyl morpholine, produced orange-colored renal casts somewhat resembling those of hemoglobinuric lower nephron disease, but again no inflammatory or necrotizing phase was noted during the first forty-eight hours; the mechanism of the production of these casts is not known.

None of the six nonmustards produced this lesion, so that tentatively the mustard structure must be considered essential for its production by compounds of this group. Further, a relatively high proportion of the mono 2-chloroethyl mustards studied produced this effect, and the bis 2-chloroethyl mustards which produced it were either tetrakis compounds or tended to have relatively large (butyl) alkyl groups as the third substituent of the amine nitrogen.

Adrenal. A mild degree of lipoid depletion was relatively common and has not been included in the table because of inability to make any significant correlations with it. The lymphoid damage produced by these compounds is known not to be mediated by adrenal cortical-hormone release or hypersecretion.[13] No mitotic or other nuclear abnormalities were observed in the adrenals.

Testis. Moderate testicular damage (++) was observed to follow exposure to ten of these nitrogen mustards (compounds, 1, 9, 10, 15, 18, 22, 26, 27, 29, 30); less significant or questionable changes were observed after fourteen others, and after two of the six nonmustards studied, and were thus felt to be nonspecific.

The testicular changes appeared to be identical for all these compounds; they were studied in detail for tris (2-chloroethyl) amine, methyl-bis (2-chloroethyl) amine, and 2-chloroethyl morpholine, and will be reported in greater detail elsewhere.[11] They consisted of pyknosis, mitotic arrest, disruption of the

spermatogenic layers, and sloughing and fusion of spermatogenic cells; these changes differed in rate of progression and in sequence, but apparently not in nature, from the testicular lesions known to follow roentgen-ray radiation, metabolite deficiency, estrogen administration, and exposure to a large number of other physical and chemical influences.

Of these compounds, 2-chloroethyl morpholine produced the most severe testicular damage, but the effect is (by the definition of a ++ lesion, which requires fusion of spermatocytes to be present) dependent primarily on an adequate survival time. As can be seen, all ten of these compounds are mustards, and all except 2-chloroethyl morpholine have two or more 2-chloroethyl side chains. There appears to be no correlation between the LD_{50} value and the ability to produce testicular damage. The testis, like the lymphoid system, is very sensitive to toxic chemicals, and the milder degrees of damage (pyknosis or shrinking of spermatocytes, arrest of maturation of spermatids) are almost completely nonspecific. However, the reason why many adequately toxic mustards did not produce more severe testicular damage in this study is obscure, and data which might provide useful correlations in this regard, as enzyme-inhibition values, do not exist.

Gastrointestinal Tract. The changes in the gastrointestinal tract produced by these compounds consist of an altered rate of mucus secretion, cytological changes in the epithelial cells at the bases of the glands, and occasionally of ulceration; in addition, the Peyer's patches shared in the damage to the lymphoid system. The compounds producing the various changes in the gastrointestinal tract are: increased mucus: 1, 6, 9, 12, 31, 33; decreased mucus: 32, 36; epithelial changes: 9, 10, 11, 12, 13, 16, 21, 30, 33; ulcers: 12, 13, 33.

The incidence of nuclear swelling or fragmentation in the epithelial cells at the bases of the intestinal glands or crypts probably furnishes a more reliable indication of the direct gastrointestinal effect of these compounds than do changes in mucus secretion, since the microscopic recognition of changes in the quantity of mucus secretion is grossly nonquantitative. These cell changes were observed with nine of the mustards and none of the nonmustards. Actual intestinal ulceration, with mucosal and/or submucosal inflammation, was observed with three of these nine compounds; it was felt in all three to be an extension of the changes in the epithelial cells, rather than secondary to rupture of a damaged Peyer's patch, or to other possible sequences.

Diarrhea, of very common occurrence after parenteral administration of nitrogen mustards, is presumably due in part to the effects listed, in part to less specific systemic toxic effects, and probably in part also to nervous-system effects [methyl-bis (2-chloroethyl) amine for example, being known to have anticholinesterase activity[1]]. Thus it cannot be correlated closely with the incidence of microscopically visible lesions, and, in fact, often precedes them.

As can be seen, a bis (2-chloroethyl) amine structure with the third N-bond hydrogen or aliphatically substituted seems to be essential for the cytotoxic action on the epithelial cells of the gastrointestinal mucosa, no compounds with mono or tris 2-chloroethyl structures being included, but no reason presents itself to explain why many compounds with a similarly substituted bis (2-chloroethyl) amine nucleus (e.g. 18, 17, 27, etc.) did not produce this effect.

Brain. Three compounds [Nos. 1, 8, and diethyl (2-chloroethyl) amine] (of which only Nos. 1 and 8 have been studied for systemic pathology) produced central-nervous-system symptoms of such severity and duration that further investigation was undertaken. The nature of the symptoms, which were essentially the same for all three compounds, has been reported elsewhere.[10] Pathological studies show that these three mustards, all of which are mono (2-chloroethyl) amines, produce two types of lesions. One consists of multiple focal glioses of the brain stem, particularly the dorsolateral portions of the hindbrain, and the other of necrosis of cells in the granular layer of the cerebellar folia. Both lesions are

thus somewhat localized, and both appear adequate to explain the vestibular-like disturbances of behavior noted, since the focal gliosis produced by these compounds involved the restiform body, the vestibular nuclei, and the tectospinal, descending spinocerebellar, and lateral pyramidal tracts, and the cerebellar necrosis appeared to be chiefly in the posterior lobe. These central-nervous-system effects will be reported in greater detail in the future.

Other Lesions. One compound, propane, 1-phenyl-1-chloro-2-[methyl (2-chloroethyl) amine], produced sufficient peritoneal irritation to permit a microscopic diagnosis of peripancreatitis, retroperitonitis, and peritonitis, and, in addition, caused the appearance of large amounts of peritoneal fluid; cell blocks of the fluid showed much protein but no cells, and there were no evidences of hepatic, cardiac, or renal damage adequate to produce ascites, so that the phenomenon may be the result of a direct effect on the vessels of the peritoneal surfaces.

Liver, pancreas, and heart, were examined in all animals, but significant lesions were never seen. The thyroid was examined in a number of cases, with no pathological findings.

Summary of Pathological Effects

Throughout the analysis of the visceral lesions produced by these nitrogen mustards, it must be borne in mind, as has been pointed out, that the animals studied were sacrificed, not after a constant duration of exposure, but at a fairly constant level of morbidity, and that variations in the relative rates of onset and progression of the lesions in the various organs may well account for some of the differences described.

Of the thirty-four nitrogen mustards and six related compounds studied for systemic pathology in this program, ten mustards and all six related compounds produced no lesion rated higher than + (mild) in any organ, under the conditions given in Table 1. These compounds are: mustards: 2, 4, 5, 6, 7, 19, 21, 25, 28; and nonmustards: 35, 36, 37, 38, 39, 40.

This table indicates the cytotoxic activity of the 2-chloroethyl amine structure, since all six nonmustards studied produced insignificant tissue damage. The reason that adequately toxic and structurally eligible mustards did not produce significant visceral damage under the conditions of this study is obscure, but it may be related to other mechanisms of toxic action, or to differences in physical or chemical properties, on which adequate data for satisfactory analysis are not now available.

Ten mustards (8, 9, 10, 11, 12, 17, 22, 23, 31, 33) produced grade ++ damage in only one organ (counting the lymphoid tissues as only one), and two compounds (3, 16) grade +++ damage in only one organ.

Twelve mustards (1, 13, 14, 15, 18, 20, 24, 20, 26, 27, 29, 30, 34) produced moderate or severe damage to two or more systems under the conditions of this study.

Again, these are all compounds with two or more 2-chloroethyl groups with the exception of 2-chloroethyl morpholine, which does not produce typical nitrogen-mustard effects. There seem to be no significant differences between the systemic effects of these nitrogen mustards causing moderate or severe damage to more than one organ, hence it would seem that the conclusion to be drawn from this study is that all adequately toxic mustards are able to damage all the susceptible organs, side effects being equal. The microscopic estimation of degrees of damage is not sufficiently quantitative so that elaborate or exacting correlations can be made from it, and the data presented in this section on general pathological effects indicate that, in general, the lesions in the organs most susceptible to nitrogen-mustard damage (lymphoid system, bone marrow, testis) are somewhat of the same order of severity for any one compound. Whether any of the twelve compounds in the second group constitute true exceptions to this rule must be determined by further studies. Variations in the order of onset of the lesions in various organs, which, over the short time periods used in this screening study, might well have resulted in the misquantitation of some effects, must be ruled out before

it can be asserted that some nitrogen mustards have a relatively selective effect on only one of the organs that tends to be damaged by compounds of this series.*

If the conclusion that all adequately toxic nitrogen mustards can produce the entire spectrum of mustard damage, if survival is sufficiently long, is correct, many nitrogen mustards other than those now being used in the treatment of malignant processes in man may have potential use, since the determining factor would seem to be the severity of the side effects at the desired dose level. Further, since in the treatment of human diseases, one is often concerned with giving a tolerated series of small doses rather than a single large dose, any one of these compounds with an equivalent acute toxicity (in terms of effect on the cells of the various sensitive viscera), but with a larger maximum tolerated cumulative dose, might theoretically be a more desirable therapeutic agent than those nitrogen mustards now in clinical use, provided the side effects were not too undesirable.

Discussion

This study attempts to determine, from the point of view of future use in the chemotherapy of human tumors, what, if any, are the correlations possible between toxicity, chemical structure, and pathological effects of the nitrogen mustards and related compounds. Thirty-four nitrogen mustards and six chemically related nonmustards are covered in this report. The pulmonary, lymphoid, bone-marrow, gastrointestinal, renal, testicular, and brain effects were the most significant pathological findings. The lymphoid organs tended to be more sensitive than the marrow; i.e., damage from the same compound was usually more severe for the lymphoid system than for the bone marrow. Severe damage to either, however, was always produced by bis or poly 2-chloroethyl compounds; this was also true of the lesions of the gastrointestinal mucosa. The testicular effects seem to be relatively nonspecific as regards chemical structure of the compound producing them. The kidney and brain effects seem to be more closely related to a mono (2-chloroethyl) amine structure, the latter tentatively to a symmetrical structure only.

As was stated in the introduction, the conclusions as to potential use in tumor therapeusis drawn from this study are based on the theory that the cytotoxic effect of the nitrogen mustards on tumors is related in some way to that on normal tissues. As has been indicated, the effects of these compounds on the lungs, kidneys, and brain do not seem to be related closely to those on the lymphoid tissues, testis, bone marrow, and gastrointestinal mucosa; compounds damaging predominantly the former organs in normal animals do not, on theoretical grounds, seem therapeutically desirable. Of the latter group of tissues, all of which resemble tumors in their relatively rapid mitosis rate, and possibly also in more fundamental biochemical factors, the lymphoid tissues and testis are felt to be too sensitive to toxic compounds (namely, they react nonspecifically to many compounds that can be assumed not to have a mustard-type action on tumors) to be considered reliable indexes of cytotoxic activity. The bone marrow and the gastrointestinal mucosa, then, seem to be the tissues from which cytotoxic activity of the mustard type can best be gauged.

There is a general correlation between the toxicity of any nitrogen mustard and the visceral damage produced by a single dose in the region of 2 LD_{50}. The reason for this phenomenon is obscure. Further, there is some evidence (bone-marrow data) that very toxic compounds are less effective in producing visceral damage than compounds of slightly lower toxicity. This may be because a certain minimal amount of drug (presumably, of molecules per cell) is necessary to produce a mustard effect; if these results are valid (bearing in mind that animals were not studied over the entire postinjection period but at only one point), an LD_{50} of 7 to 8 micro-

* The gastrointestinal-tract sections showed that essentially all the animals used in this study were infected with the tapeworm *Hymenolepis nana*. This may have an effect on the absolute values for toxicity of the various compounds but presumably does not affect the relative toxicities nor the relative effects on the viscera.

moles per Kg. would seem to be the threshold value for the production of a mustard effect on dividing cells, when the drug is administered as in this study.

Thus, for the production of the systemic mustard effect, a relatively toxic nitrogen mustard (LD_{50} of 100 or less moles per Kg. $\times 10^6$) seems more desirable than a less toxic one, although the very toxic ones (LD_{50} below 7 to 8 moles per Kg. $\times 10^6$) are probably not satisfactory. The mono (2-chloroethyl) amines (one-armed mustards) in general are less effective than the bis or poly (2-chloroethyl) amines in producing lymphoid and bone-marrow damage, and more effective in producing renal and brain damage. In fact, the bis or poly (2-chloroethyl) amine structure seems in general necessary for a true mustard effect on tissues. Further, the mono (2-chloroethyl) amines (one-armed mustards), because of their tendency to damage kidney and brain (which do not regenerate so well as marrow, lymphoid tissue, and the other more rapidly dividing tissues), do not seem potentially useful as chemotherapeutic agents for human tumors. The nonmustards studied in this program produced no significant effects, and give no evidence that compounds of this type (tetraalkyl-ammonium compounds, ethanolamines, amines) possess chemotherapeutic possibilities.

The typical mustard death is delayed (about 72 hours) and compounds killing faster than this (many of the more toxic ones) are probably acting by other methods. One would expect competition for the drug between the mustard effect and any side effects to be more significant with the more toxic compounds, which are given in smaller doses; this may explain the lack of cytotoxic effect of some of the very toxic mustards.

This study suggests that all the satisfactory mustards, as regards cytotoxic effects (in terms of these effects, and thus in terms of dosage), have the same effects, side actions being equal and survival adequate. Hence, within this group, the factor determining the choice of an agent for the chemotherapy of tumors would seem to be the relative severity of any side effects as compared to the mustard effects. Within the group of nitrogen mustards with desirable LD_{50}'s and pathological effects, and with relatively minor side effects, the compound of choice as a tumor chemotherapeutic would seem to be the one with the largest tolerated cumulative dose. Data on this point are in preparation but are not yet available. Hence, the nitrogen mustards now in common clinical use for the chemotherapy of tumors [tris (2-chloroethyl) amine, methyl-bis (2-chloroethyl) amine, ethyl (2-chloroethyl) amine] may very well not be the best nitrogen mustards for this purpose. When data on the cumulative toxicity of this series of agents are available, and when more poly 2-chloroethyl nitrogen mustards are synthesized, more effective nitrogen mustards for tumor chemotherapy may very well be found.

As has been pointed out above, the theory on which this study is based is that the cytotoxic effect of the mustards on tumors is related to their cytotoxic effect on normal tissues with rapidly dividing cells. If this theory is valid, the use of nitrogen mustards in the chemotherapy of tumors must depend on a therapeutic ratio between the effect on the tumor and the undesirable effect on the normal tissues of the patient, rather than on an absolute therapeutic effect. This is also true for radiation therapy of tumors (whether by roentgen rays, radium and radon, or radioactive isotopes), and clinical experience has so far indicated that it is true for the nitrogen mustards used clinically to date.[2, 3, 4, 5, 7, 8, 12]

Summary

The pathological effects produced by thirty-four nitrogen mustards and six chemically related nonmustards are reported, and a comparative analysis of the chemical structure, toxicity, and degree of effect on the various organs is presented. As a result of this analysis, it was found that nitrogen mustards with two or more (2-chloroethyl) side chains, and with median lethal doses from 10 to 1000 micromoles per Kg., are the ones most cytotoxic to rapidly proliferating cells, and it is

suggested that nitrogen mustards of this type have the greatest potential utility in the chemotherapy of human tumors. Within this group of compounds, those with larger maximum tolerated cumulative doses and minor side effects would seem on theoretical grounds of most potential value in tumor chemotherapeusis.

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THE EFFECTS OF A NITROGEN MUSTARD [TRIS (2-CHLOROETHYL) AMINE] ON REGENERATING RAT LIVER

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IN a previous study on the systemic pathological effects of a series of nitrogen mustards,[10] it was found that normal mouse liver shows no microscopic changes following parenteral administration of single doses as large as twice the median lethal dose. However, since the nitrogen mustards are known to exert their cytotoxic effects predominantly on tissues with relatively rapid rates of cell division (bone marrow, lymphoid tissue, gastrointestinal epithelium, and testis), a possible explanation for the apparent immunity of normal liver was thought to lie in its low rate of cell division. To test this hypothesis, regenerating liver, which has as high a mitosis rate as any of the organs just listed, was used. In addition to having a high mitosis rate, the regenerating liver offered the added advantage of a uniform cell type, so that studies conducted at varying intervals after partial hepatectomy afforded control of the stage of cell reproduction present at the time treatment was given. Tris (2-chloroethyl) amine (HN3) was chosen for these experiments because it is known to exert a powerful cytotoxic effect.

METHODS

Wistar white rats of both sexes, weighing 150 to 300 gm., were partially hepatectomized by the technique previously described by Higgins and Anderson, Brues, Drury, and Brues,[4] and others. A study on twenty-five unselected rats showed the ratio of weight of liver left in at operation to that taken out to be 0.463, a value similar to that found by previous workers.

The nitrogen mustard was administered at varying intervals after operation by injection into a tail vein of 1.4 mg. per Kg. of HN3·HCl [tris (2-chloroethyl) amine] as a solution of 0.5 mg. per cc. in normal saline. This is twice the median lethal dose.[1] The solutions were made up fresh before every group of injections. At various time intervals after operation, the rats were etherized and killed by exsanguination.

The livers removed at operation were fixed in 10 per cent formalin. Those removed at the time of sacrifice were fixed by two different methods: (1) freezing in dry-ice acetone, and fixation in 10 per cent formalin at 0°C.; (2) perfusion with neutral 10 per cent formalin in saline via a plastic catheter inserted into the portal vein through a 17-gauge needle. At the same time periods, comparative studies showed no recognizable difference in the mitosis rates of livers treated by these two methods. The second method was used for the great majority of the animals.

The volumes of the livers removed at operation and at autopsy were determined in one of two ways:

1. The liver was weighed after fixation and sliced with a double-edged knife with a known distance between the blades. From these slices, sections were punched with a cork borer of known diameter and the average weight of three such cylinders determined. Since the volume of these punches was known, the volume of the fixed liver could be calculated, assuming the volumes to be in the same proportion as the weights.

2. After fixation, the volume was determined directly by a fluid-displacement

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apparatus consisting of a ground-glass jointed chamber connected above with a burette and below, through rubber tubing, to a leveling bulb. The system was filled with water and the water level brought to a mark on the stem of the leveling bulb. A reading from the burette was taken and the water level lowered below the jointed chamber. The liver was placed in the chamber, the water level brought back to the mark on the stem of the leveling bulb, and a second reading on the burette taken. The difference in the two burette readings was equal to the volume of the liver. Successive measurements usually checked within 0.1 cc. Standard punches were then made, but not weighed.

The standard punches of all livers were embedded in paraffin, sectioned at 6 to 10 microns and stained with hematoxylin and eosin. The section was then projected on a calibrated screen, and the greatest and least diameter measured. These values were averaged and divided by the diameter of the standard punch to give an average linear shrinkage factor that was cubed to give a volumetric shrinkage factor. The thickness of the section was determined with the fine-adjustment micrometer scale on the microscope by focusing on the upper and lower edges. The average of three such determinations was used.

The number of cells per unit volume was determined by counting the number of nuclei visible in a calibrated area covered by an ocular reticle. Five such determinations were made for each liver and averaged. Since the nuclei within the reticle included those whose centers lay within an average of one-half nuclear diameter above and below the section, the thickness actually represented included the thickness of the section plus one nuclear diameter. The average nuclear diameter for each section was determined by measuring forty nuclei with a calibrated ocular micrometer.

The fat present at any time was determined by quantitating each slide for fat content, up to 2 plus as a maximum, and averaging the values for the animals at each point.

The cell volume was determined by dividing the total volume of the fixed liver by the number of cells. This assumes that the volume of the extracellular space is negligible in comparison to the intracellular space. How valid this is after perfusing a liver and allowing it to remain an additional twenty-four to forty-eight hours in formalin is debatable. In viewing the per cent changes in cell volume, it is well to remember that the livers removed at operation were not perfused with formalin saline, whereas those removed when the animal was sacrificed were perfused. Hence, per cent increases in cell volume are apt to be high, but comparative changes in cell volume between control and treated groups should be valid.

The nuclear volume was determined from the nuclear diameter by the formula for the volume of a sphere, $\frac{1}{6}\pi d^3$, assuming that the nuclei shrank as much as the whole liver, and correcting the nuclear volume by the shrinkage factor. This assumption may not be correct but, again, changes between groups in the per-cent increase in nuclear volume should be valid.

The mitosis rate and differential mitosis count were determined by counting 1000 cells in each section. The resting mitosis rate, and hence the presumed mitosis rate of the liver left in at operation, was determined from the first fifty livers removed at operation and found to be 0.02 per cent cells in metaphase.

The following calculations were used in this study:

1. Weight of liver removed at operation multiplied by 0.463 equals weight of liver remaining.
2. Volume of liver removed at operation multiplied by 0.463 equals volume of liver remaining.
3. Number of cells per cc. of liver =

$$\frac{NF\ (10^8)}{2.77\ (t+d)}$$

where N = volumetric shrinkage factor
t = thickness of section in microns
d = average nuclear diameter in microns

4. Per cent increase in weight, volume, total cells, nuclear volume, cell volume =

$$\left(\frac{\text{av. value at autopsy}}{\text{av. value in liver remaining at operation}} - 1\right) \times 100$$

5. The duration of mitosis may be predicted from the mitosis count and per cent increase in cells in the following manner:

Let N = number of cells at any one time.

Then $\frac{dN}{dt}$ = change of cells with time which = the rate of increase of cells = rate of entrance into mitosis.

Let M = mitosis count and T = duration of mitosis

$$\text{then } \sum_{t}^{t+T} \frac{dN}{dt} \cdot dt = \sum_{t}^{t+T} dN = \text{absolute number of dividing cells visible at any one time}$$

Assuming $\frac{dN}{dt}$ varies linearly over the duration of one mitosis

$$\text{then } \sum \frac{dN}{dt} \cdot dt = \frac{dN}{dt} \text{ (at the mid-point)} \cdot T$$

which is the entrance into mitosis per time interval multiplied by the length of time it takes for a cell to go through mitosis.

The mitosis count "M" is the absolute number of cells in mitosis divided by the total number of cells present:

$$M = \frac{\frac{dN}{dt} \cdot T}{N} \longrightarrow \frac{dN}{N} = \frac{M \cdot dt}{T}$$

Since it is not known how M varies between the various points at which it was determined, a linear function has been assumed as a best approximation.

$$M = ct + a$$

This is the equation of a straight line, where "c" equals the slope of the line during any particular time in which M is varying linearly; "a" is the M intercept when "t" equals zero.

$$\frac{dN}{N} = \frac{(ct + a)dt}{T}$$

Assuming T does not vary with time and integrating

$$\log N = \frac{1}{T}\left(\frac{ct^2}{2} + at\right) + K$$

$$N = {}_eK \cdot {}_e\frac{ct^2 + 2at}{2T}$$

This is the value for N at the end of any interval during which the slope of the mitosis-count curve is "c." If this interval started at time A and ended at time B, then let N_B equal the number of cells at the end of the interval, and N_A the number at the beginning of the interval. Then, at the beginning of the interval $t = 0$

$$N_A = {}_eK \cdot {}_e0 = {}_eK$$

$$N_B = N_A c\frac{ct^2 + 2at}{2T}$$

$$N_B - N_A = N_A c\frac{ct^2 + 2at}{2T} - N_A$$

$$\frac{N_B}{N_o} - N_A = \frac{N_A}{N_o}\left(c\frac{ct^2 + 2at}{2T} - 1\right)$$

Where N_o equals the number of cells remaining after operation

$$\frac{N_B - N_A}{N_o} \cdot 100 = \text{the per cent increment in cells for each interval}$$

The per cent increase in cells at time x =

$$\sum_{o}^{x} \frac{N_B - N_A}{N_o} \cdot 100 =$$

$$100 \sum_{o}^{x} \frac{N_A}{N_o}\left(c\frac{ct^2 + 2at}{2T} - 1\right)$$

From the form of the final equation, it is obvious that since we know "o" and "a" (both related to the mitosis count) experimentally, we can compute N if we know T, or if we know N (the experimental values) we can compute T.

This equation has the advantage over that proposed by Brues and Marble[3] in that it presupposes no particular mechanism of division, and it is applicable in any condition in which there is inhibition of entrance into mitosis or slowing of mitosis.

TABLE 1

EFFECTS OF HN3 ON REGENERATING RAT LIVER

Hrs. after operation when killed	*No. animals*	*Av. wt. at operation gm.*	*Av. wt. of liver left at operation gm.*	*Av. vol. of liver left at operation cc.*	*Av. no. cells left* $\times 10^8$	*Av. nuclear vol. at operation* $cc. \times 10^{-11}$	*Incr. in liver wt.* %	*Incr. in liver vol.* %	*Incr. in cells* %	*Incr. in cell vol.* %	*Incr. in nuclear vol.* %
Control											
12	7	200	2.4	2.7	2.2	31	9	4	15	−10	60
24	8	170	2.1	2.3	2.0	28	40	48	25	18	62
36	9	180	2.4	2.7	1.8	35	64	68	37	23	87
48	7	171	1.8	2.0	2.1	40	130	94	66	19	29
60	3	164	2.1	2.2	1.2	38	122	126	150	−10	45
72	4	206	2.7	2.9	1.8	38	156	178	124	24	35
96	5	228		2.8	2.0	39		190	113	36	31
HN3 Injected at Time of Partial Hepatectomy											
36	5	180	2.4	2.8	2.0	44	75	84	27	40	92
48	4	220	4.0	4.4	2.2	46	64	74	46	19	95
60	5	234	3.2	3.7	2.1	41	61	64	38*	19	81
HN3 Injected 12 Hours after Partial Hepatectomy											
36	5	180	2.1	2.4	2.0	37	91	111	34	57	104
48	5	173	2.0	2.2	2.0	34	124	133	106	13	60
60	2	240	3.2	3.8	2.2	38	89	80	73	4	136
HN3 Injected 24 Hours after Partial Hepatectomy											
36	5	170	2.2	2.3	1.6	30	69	89	49	27	100
48	6	174	2.1	2.7	2.3	33	110	111	12	88	67
HN3 Injected 36 Hours after Partial Hepatectomy											
48	9	202	3.0	3.6	2.0	42	89	96	36	44	76
60	5	166	2.2	2.6	1.9	40	91	96	48*	32	53
72	4	206	3.0	3.4	2.0	43	102	94	70	14	128
84	4	250	3.1	3.6	2.1	52	101	99	93	3	45
96	5	241	3.5	4.1	2.2	48	87	88	122	−28	46

* Refers to values that are significantly different from control values. Only increase in cells and cells in mitosis have been statistically analyzed.

RESULTS

The data are presented in Tables 1 and 2, and Figs. 1, 2, and 3. Since there is considerable variation among the individual values in this study, slight increases or decreases in the averages are not significant. The significant differences between control and injected animals have been determined for the mitosis counts and the per cent increase in cells. These values have been starred in Tables 1 and 2. The variability is especially noticeable in the values for the sixty-hour controls, in which only three animals were used to determine the average. The apparent decrease in cells which can be noted for several groups of animals in Fig. 2 is not statistically significant. No morphological or other evidence that HN3 at any time causes a lysis or disappearance of liver cells was obtained in this study.

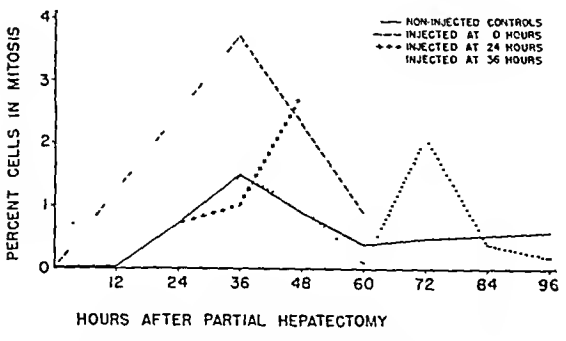

FIG. 1. *Effect of 1.4 mg. per Kg. of HN3 intravenously on the mitosis count in regenerating liver.*

Injection at Time of Operation. When twice the median lethal dose of HN3 was injected intravenously at the time of operation, the mitosis count was twice the control value (Fig. 1) thirty-six hours later. This difference is statistically significant (probability of 0.05), shown by an analysis of the difference between the means. The apparent reason for the high mitosis count is a slowing of the process of mitosis. The duration of mitosis, calculated

TABLE 2

EFFECTS OF HN3 ON REGENERATING RAT LIVER

Hrs. after operation when killed	*Cells in mitosis* %	*Differential mitosis count*					
		Prophase %	*Metaphase* %	*Anaphase* %	*Telophase* %	*Reconstruction* %	*Fat (micro. estimation)*
Control							
12	.06	.01	0	.03	0	0	.6
24	.82	.13	.29	.18	.14	.08	.9
36	1.61	.28	.57	.31	.24	.21	.9
48	1.03	.07	.62	.20	.11	.04	.8
60	.38	.08	.22	.07	.03	0	1.3
72	.51	.06	.29	.06	.04	.06	1.0
96	.64	0	.26	.08	.20	.10	.1
HN3 Injected at Time of Partial Hepatectomy							
36	3.71*	.46	1.06	.71	.84	.64	.8
48	2.28	.50	.70	.22	.30	.52	.4
60	.90	.10	.32	.20	.12	.14	.8
HN3 Injected 12 Hours after Partial Hepatectomy							
36	2.53	.34	.94	.55	.50	.19	1.2
48	1.21	.28	.57	.18	.16	.04	1.6
60	.68	0	.23	.10	.13	.20	.7
HN3 Injected 24 Hours after Partial Hepatectomy							
36	.95	.07	.48	.06	.21	.13	1.9
48	2.63*	.61	.87	.38	.47	.31	1.6
HN3 Injected 36 Hours after Partial Hepatectomy							
48	1.04	.16	.41	.12	.21	.14	.8
60	.10	.02	.04	0	.04	0	.6
72	2.10*	.18	.86	.20	.42	.38	.4
84	.38	.03	.13	.03	.10	.10	.2
96	.18	.04	0	.02	.08	.02	.4

* Refers to values which are significantly different from control values. Only increase in cells and cells in mitosis have been statistically analyzed.

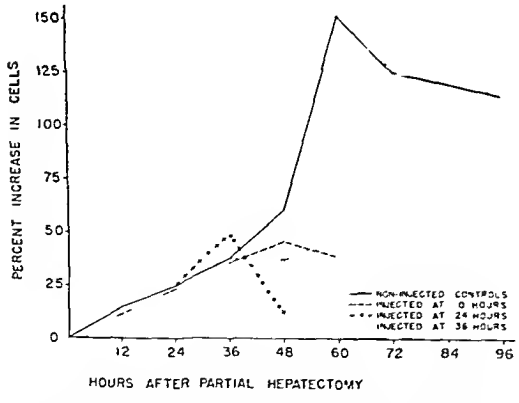

FIG. 2. *Effect of 1.4 mg. per Kg. of HN3 intravenously on the increase in cells in regenerating liver.*

by the equation given under methods, is 300 minutes for the period twenty-four to thirty-six hours and 150 minutes for the period thirty-six to forty-eight hours. In contrast, the duration of mitosis in the control animals in this series is approximately forty-five minutes (Fig. 4).

The differential mitosis count in the treated group is the same as in the control group, an indication that no particular stage of mitosis is affected by the HN3 administration. All stages of mitosis are slowed equally.

Any decrease in the number of cells below control values means that fewer cells have entered mitosis in the treated group than in the controls. The number of cells at sixty hours is significantly less than in the controls, and hence there has been some inhibition of entrance into mitosis (Fig. 2). However, the significance is not great, and it is hard to tell from our data just when inhibition began and how long it lasted.

In all groups of animals, treated and controls, there is a general correlation between mitosis count and nuclear volume—these increase and decrease together. The interpretation given is that the nucleus enlarges in cells about to divide, a high nuclear volume

indicating a large number of cells about to divide as well as already dividing.

Injection Twelve Hours after Operation. The results in this group are essentially the same as in the group injected at operation.

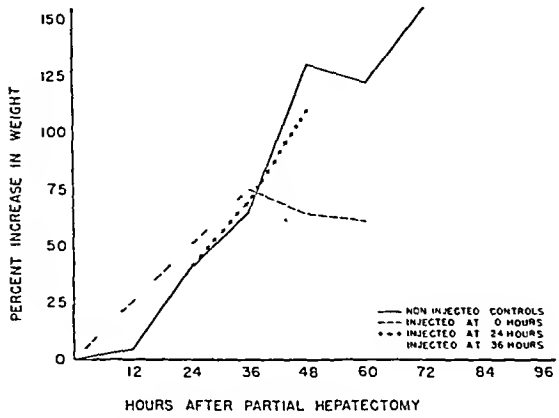

FIG. 3. *Effect of 1.4 mg. per Kg. of HN3 intravenously on the weight of regenerating liver.*

Injection Twenty-four Hours after Operation. The mitosis count in this group is highest at forty-eight hours after operation or twelve hours later than in the control group. There is no increase in cells corresponding to the high mitosis rate and hence slowing of the process of mitosis must be assumed. Again there is questionable evidence of inhibition of entrance into mitosis. The mitosis count and per cent increase in cells at thirty-six hours after operation are the same as the control values. It is only at forty-eight hours that they diverge.

Injection at Thirty-six Hours after Operation. The animals injected thirty-six hours after operation also show slowing of the process of mitosis. Averaging the increments in per cent increase in cells between thirty-six and sixty hours in the treated group, and using this average and the corresponding mitosis counts to calculate the duration of mitosis, one finds that the duration was 220 minutes during the interval thirty-six to forty-eight hours and 110 during the interval forty-eight to sixty hours; the control value was forty-five minutes. During succeeding periods, the duration of mitosis averaged fifty minutes for the treated animals. The effect of HN3 in lengthening the duration of mitosis is then primarily present for only twenty-four hours after injection in this group of animals in contrast to thirty-six to forty-eight hours in the group injected at the time of operation.

The per cent increase in cells is significantly below the control values at sixty hours. Here the data seem to indicate that there has been an inhibition of entrance into mitosis that lasts twenty-four hours after injection. At the end of this twenty-four hours, the per cent increase in cells rises at a rate comparable to the controls at thirty-six hours, indicating that cells are entering mitosis at the same rate in both groups.

The peak in the mitosis-count curve at seventy-two hours, in the animals injected at thirty-six hours, is a reflection of escape from inhibition of entrance into mitosis.

The liver weights (Fig. 3) and cell volumes of the animals injected thirty-six hours after operation tend to fall below control values around the third and fourth days, an effect in all probability caused by lack of appetite and the general debility produced by systemic mustard poisoning.

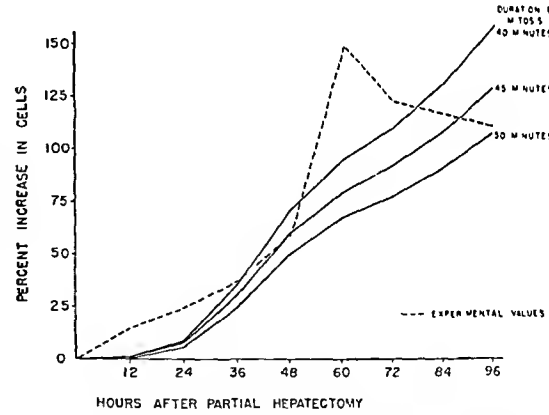

FIG. 4. *Increase in cells calculated from the mitosis counts—control animals.*

Miscellaneous Observations. In addition to noting the effects of this agent on the liver, other organs were removed at the time of sacrifice and examined for the presence of nitrogen-mustard effects. The most noticeable effect was a disappearance of lymphoid cells from the spleen beginning at twelve hours and becoming more marked by thirty-six hours.

There was no evidence of inflammation in the livers of either control or HN3-treated animals. Two animals in this series happened to have numerous granulomas of the liver, the lymphocytic cells of which completely disappeared after treatment, leaving only the fibroblastic stroma. These animals were used only for mitosis counts and not included in the column "number of animals" in Table 1. It is also to be noted that the Kupffer cells showed pyknosis and degeneration, most marked twenty-four to forty-eight hours after injection.

No evidence was found of the large increase in nuclear volume observed by Bodenstein in salamander embryos raised in an environment of methyl-bis (2-chloroethyl) amine or by Friedenwald, Buschke, and Scholz[6] in the cornea on repeated application of the methyl-bis (2-chloroethyl) amine. It is to be noted, however, that repeated doses were not given in this study. No evidence was found of nuclear pyknosis such as observed by Landing[9] in the testis or of degeneration such as found by Kindred for lymphocytes. Fragmentation of the nucleus observed by Friedenwald and Buschke[5] in the cornea up to six hours after one drop of 0.03 per cent methyl-bis (2-chloroethyl) amine was not seen in the liver. However, in this study, the livers were not examined earlier than twelve hours after injection, and the dose used, calculated on the basis of 20 per cent extracellular fluid by weight, would only be 0.0006 per cent.

The values obtained by Brues, Drury, and Brues[4] for the per-cent increase in volume (measured after paraffin embedding) are: 57 per cent at twenty-four hours, 121 per cent at forty-eight hours, 150 per cent at seventy-two hours, and 157 per cent at ninety-six hours. Their values for the per cent increase in cells are: 6 per cent at twenty-four hours, 65 per cent at forty-eight hours, 107 per cent at seventy-two hours, and 128 per cent at ninety-six hours. The values of Brues and Marble[3] for the number of cells in mitosis at time of sacrifice are: 2.13 per cent at twenty-four hours, 0.97 per cent at forty-eight hours, 0.63 per cent at seventy-two hours. The difference between the values obtained in this study for the mitosis count at twenty-four hours (0.82 per cent) and Brues and Marble's is statistically significant. All other mitosis-count values are in perfect agreement. Perhaps differences in operative technique might affect the twenty-four–hour mitosis count.

If the equation presented under methods relating mitosis count, duration of mitosis, and number of cells is applied to the data of Brues et al., a perfect fit is obtained, providing the duration of mitosis is taken as fifty minutes and the increase in mitosis count taken as starting at nineteen and a quarter hours after operation.

Comparison of the Effects of HN3 on Regenerating Rat Liver and on Other Tissues. In the corneal epithelium, according to Friedenwald, Buschke, and Scholz,[6] the predominant effect of methyl-bis (2-chloroethyl) amine is to inhibit entrance into mitosis. With a subcutaneous LD_{50} dose, they were unable to observe any slowing of the mitotic process once it had begun.

Kindred studied the effects of the nitrogen mustards on lymphoid tissue and noted that the reticulum cells of lymphoid tissue were only slightly affected. There was inhibition of entrance into mitosis of all lymphocytes and some degeneration of lymphocytes. Recovery from the inhibition of entrance into mitosis began to occur around three days after injection.

In bone marrow, the nitrogen mustards produce diminution of the number of cells. This is associated with, but not caused by, inhibition of entrance into mitosis.[8] The actual mechanism of the loss of the hematopoietic cells has not been established. All the cells of the marrow are affected, the megakaryocytes possibly less than the others. Recovery begins in two to three days.

In the gastrointestinal tract, swelling, pyknosis, and vacuolation of the epithelial cells in the crypts of the intestinal glands takes place and the total number of epithelial cells decreases. Whether or not the normal process of sloughing of epithelial cells is accelerated has not been studied. Occasionally, ulceration occurs, which seems most probably to

result from the action of the nitrogen mustard on the dividing cells of the glands.

In the testis,[9] the nitrogen mustards cause transitory inhibition of mitosis, pyknosis, and lysis of cells, followed by desquamation.

Summary

1. The effect on the regenerating rat liver of the intravenous administration of 1.4 mg. per Kg. of the nitrogen mustard, tris (2-chloroethyl) amine, has been studied.

2. The nitrogen mustard slows the process of mitosis. The effect is present thirty-six to forty-eight hours after injection, when the injection is made at the time of partial hepatectomy, and for twenty-four hours after injection when the injection is made thirty-six hours after partial hepatectomy.

3. There is some evidence of inhibition of entrance into mitosis. The effect is most noticeable in animals injected thirty-six hours after partial hepatectomy, and lasts for 24 hours.

4. The relative immunity of normal liver to the cytotoxic effects of the nitrogen mustards is not the result of a low mitosis rate, since the immunity is still apparent when the liver is dividing rapidly.

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TESTICULAR LESIONS IN MICE FOLLOWING PARENTERAL ADMINISTRATION OF NITROGEN MUSTARDS*

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WITH THE TECHNICAL ASSISTANCE OF
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BENJAMIN GOLDBERG, PH.D., and ARTHUR J. FISK

ALTHOUGH 2-chloroethyl–substituted compounds (mustards) have long been known to exert much of their systemic toxic effect on rapidly dividing cells, and testicular lesions have been observed to follow exposure to mustard gas (bis (2-chloroethyl) sulfide), no systematic studies on the nature of the testicular lesions produced by nitrogen mustards (2-chloroethyl–substituted amines), on their severity, and on the rate and degree of recovery from them, have been published. A study of the acute and chronic testicular effects of some of the nitrogen mustards seemed desirable, since these compounds are now being used in the chemotherapy of malignant processes in man.

METHODS

Adult male (20 gm.) Carworth Farm mice were given varying doses of the various nitrogen mustards by intraperitoneal injection. The drugs were given in normal saline, drug and diluent together making 1 per cent of the body weight. The testes were removed at various times after injection and fixed immediately in acidified Zenker's solution. Sections were embedded in paraffin, sectioned at 5 micra, and stained with hematoxylin and eosin.

For the study of the occurrence of testicular lesions following exposure to the various compounds, one section of each testis was studied from each of four animals for each compound used. For the more detailed studies on the nature and pathogenesis of the lesions, four to ten adjacent sections were cut through the greatest longitudinal dimension of one testis from each animal used, and a similar number from the greatest transverse diameter of the other; although both sets of sections were used for the study of the cellular changes, only the longitudinal sections were used for the assessment of the degree of damage. Control animals were chosen at random; one group was killed immediately; a second was fasted, but given water, for twenty-four hours; and a third group was similarly fasted for forty-eight hours.

INTERPRETATION OF RESULTS

Normal Histology of the Young Adult Mouse Testis. Sections of the testes of untreated control animals showed complete conformity with previous descriptions of the histology of the mouse testis.[1, 10, 14] (Fig. 1.)

Estimation of Degree of Damage. Attempts have been made by Mason, and von Wattenwyl and Joel, to devise methods that give a quantitative estimate of the degree of damage to a mammalian testis following exposure to a "toxic factor." Both methods involve the numerical evaluation of the tubule appearances seen during the course of the degenera-

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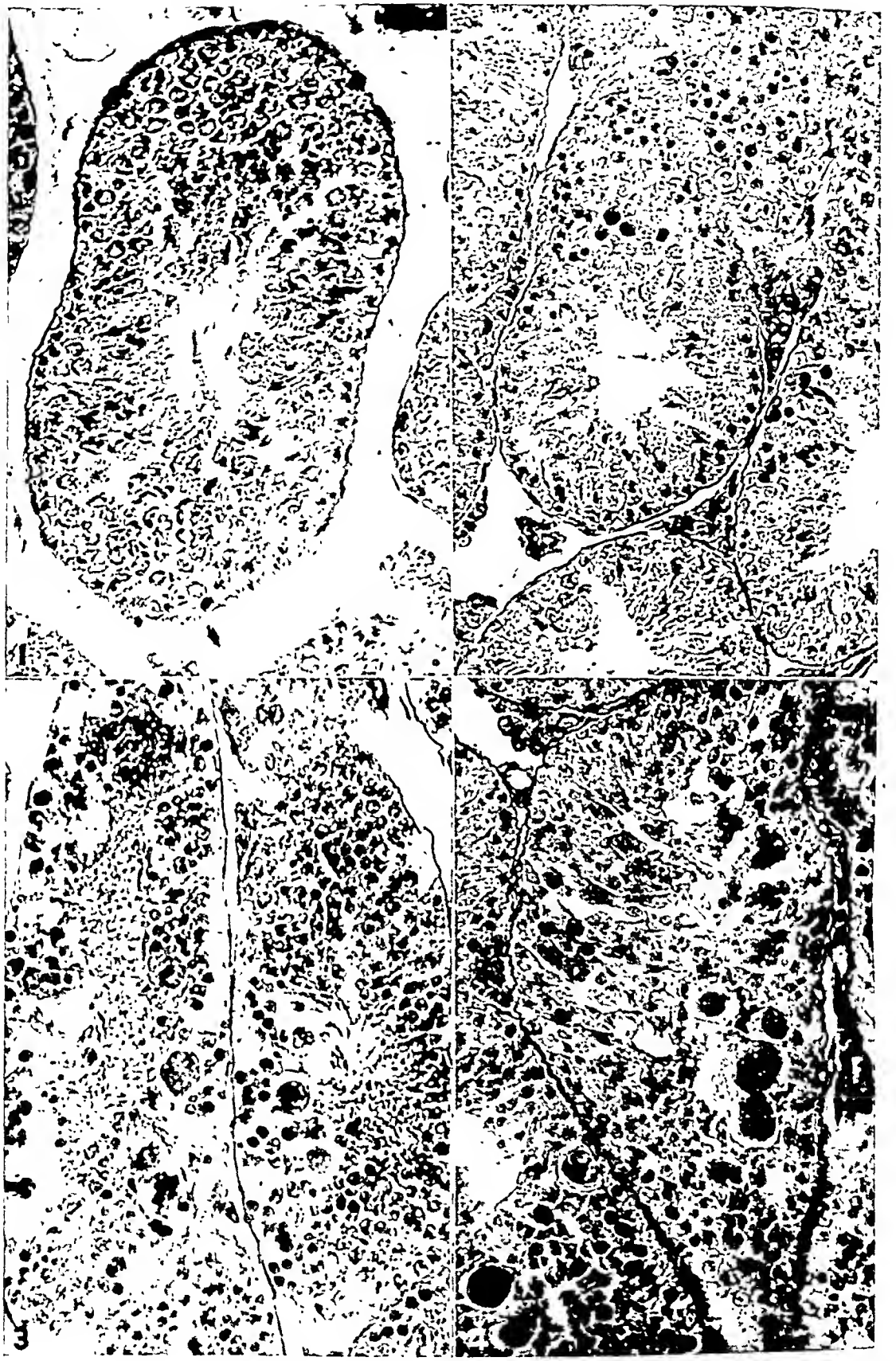

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tive process and were devised for, and applied to, relatively slow degenerative processes (vitamin deficiency and roentgen-ray radiation respectively).[7, 12] They require a uniformity of tubular appearance that does not exist in the normal or in the acutely damaged young adult mouse testis.

Because of the variation in the cell population of different tubules, counts of the relative numbers of normal and abnormal spermatogenic cells of all types seen in a standard area are not reliable quantitative indexes of damage. In this study, an estimate of the degree of damage to each testis was obtained by counting the number of tubules containing abnormal spermatogenic cells of any type seen on the periphery of a standard longitudinal testis section. This value was multiplied by a factor expressing the average severity of the damage to each of the damaged tubules (expressed as 1,2,3, for mild, moderate, and severe) to give an Index of Injury. The average number of tubules counted on the periphery of the longitudinal sections was 40, so that 120 was the highest possible Index of Injury that could be produced.

This method of assessing the degree of damage to the testis involves a subjective factor and assumes that the incidence of visibly damaged tubules is uniform throughout the testis, or at least that the damaged tubules counted have some constant relationship to those of the rest of the tesis. How nearly this can be held true is not known, but except for the animals studied late after repeated doses of methyl-bis (2-chloroethyl) amine, at which time the peripheral tubules in the sections did show more damage than the central ones, the pattern of tubular damage appeared to be the same in all areas of the testes studied. Normal testes contain a small number of recognizably abnormal spermatogenic cells, but, by the earliest time studied, testes from animals receiving a nitrogen mustard showed a greater number of abnormal cells of a different type.

TABLE 1

NITROGEN MUSTARDS OBSERVED* TO PRODUCE SIGNIFICANT TESTICULAR LESIONS

Formula†	LD_{50} (*mg./Kg.*)
Tris (2-chloroethyl) amine	2.02 ± 0.26
Methyl-bis (2-chloroethyl) amine	4.13 ± 0.37
i-Propyl-bis (2-chloroethyl) amine	1.33 ± 0.12
2-Chloroethyl morpholine	161 ± 6.
i-Butyl-bis (2-chloroethyl) amine	4.42 ± 0.34
N,N,N',N'-tetrakis (2-chloroethyl) ethylene diamine	16.4 ± 0.6
Phenyl-bis (2-chloroethyl-mercaptoethyl) amine	691.0 ±50.
3-Chlorobutyl-bis (2-chloroethyl) amine	8.13 ± 0.80
2-Chloroallyl-bis (2-chloroethyl) amine	19.3 ± 1.6

* These compounds were obtained from the University of Chicago Toxicity Laboratory.

† All compounds were used in the form of the hydrochloride salt.

RESULTS

Occurrence of Testicular Lesions Following Exposure to Nitrogen Mustards. Testicular lesions were found at autopsy forty-eight hours following the intraperitoneal injection of two previously determined median lethal doses (LD_{50}) of the following nine nitrogen mustards. Approximately twenty-five other nitrogen mustards produced either less significant or no testicular lesions after comparable exposures.

PATHOLOGICAL CHANGES FOLLOWING NITROGEN MUSTARDS

The lesions observed were studied in greater detail for three of these compounds:

FIG. 1. *Section of normal mouse testicular tubule, showing cell layers of spermatogenic epithelium.*

FIG. 2. *Twenty-four hours after injection of 4.0 mg./Kg. of methyl-bis (2-chloroethyl) amine. Note relative absence of spermatozoa and numbers of pyknotic cells.*

FIG. 3. *Thirty-eight hours after injection of 4.0 mg./Kg. of methyl-bis (2-chloroethyl) amine. Note pyknotic cells, clefts and spaces in spermatogenic layers, and early stages of formation of fusion giant cells.*

FIG. 4. *Seventy-two hours after injection of 4.0 mg./Kg. of methyl-bis (2-chloroethyl) amine. Note numbers of fusion giant cells, and sloughing of the epithelium.*

tris (2-chloroethyl) amine, methyl-bis (2-chloroethyl) amine, and 2-chloroethyl morpholine, by examination of testes from exposed animals at varying times after injection of various doses of the compounds.

Table 2 lists the doses of the three mustards used, in mg. per Kg. and in percentage of the previously determined LD_{50} (for intraperitoneal injection into this strain of mouse), and the degree of testicular damage present at the various times after injection in terms of the average Indexes of Injury of the animals studied at each time.

The earliest microscopic changes noted in mouse testes after intraperitoneal injection of nitrogen-mustard solutions, all well shown within twenty-four hours after injection (Fig. 2), included thickening of the chromatin strands of many resting nuclei of spermatogonia and spermatocytes, and cytoplasm that appeared normal at first but became hyaline and eosinophilic as pyknosis progressed. The first two spermatogenic divisions (spermatogonium to primary spermatocyte, and primary to secondary spermatocyte) were most commonly affected, causing the appearance of numbers of abnormal metaphases and smaller numbers of abnormal anaphases of both these divisions. These cells showed dark, swollen chromosomes, hyaline eosinophilic cytoplasm, and loss of spindles, followed by gradual fading of the chromatin. A small number of similar cells was also found in the control testes, but the number was increased after all three nitrogen mustards studied.

Disruption and disorientation of the spermatogenic epithelium occurred in many animals within twenty-four hours after exposure, many spermatocytes came to lie free in the lumina of the tubules, and there was a marked decrease in the number of mature spermatozoa. These changes were thought to be the result of the failure of new cells to develop as damaged ones lysed or sloughed and passed down the tubules.

Later, well shown at either forty-eight or seventy-two hours (Figs. 3, 4), these changes progressed, with the production of more marked disorganization of the layers of spermatogenic cells, many tubules being loosely filled with normal and abnormal cells of various types with no orientation into layers. Many of those sloughed spermatogenic cells could also be seen in the tubules of the epididymis at this time. By forty-eight hours in most cases, fusion of secondary spermatocytes and, rarely of primary spermatocytes, to form bi- to multinucleate giant cells was seen; these cells gradually became pyknotic, with the chromatin clumped on one side of the nuclei so that these somewhat resembled spermatid nuclei (Figs. 3, 4). Fusion of spermatids is reported to occur in

TABLE 2

EFFECT OF NITROGEN-MUSTARD EXPOSURE ON MOUSE TESTIS

Values Are Average Indexes of Injury (Index of Injury = Number of Injured Tubules Times Average Degree of Damage to Injured Tubules); Mean Maximal Value of Index = 120

Drug	*Dose mg./Kg.*	*Dose fraction of LD_{50}*	*Days after injection*												*Total animals*
			1	*2*	*3*	*5*	*8*	*13*	*17*	*20*	*23*	*27*	*30*	*36*	
Normal controls			4.5												9
Fasted controls			5.6												5
Methyl-bis (2-chloroethyl) amine	4.0	.95	14	26	8	11	14			6					12
Methyl-bis (2-chloroethyl) amine	6.3	1.4	6	18	21	55	31	No survivors							10
Methyl-bis (2-chloroethyl) amine	0.6 for 7 inj.'s	.14×7		14	22			6	6	[71	51	60	85]*		15
Tris (2-chloroethyl) amine	1.5	.74	10	38	6	14	27	No survivors							10
Tris (2-chloroethyl) amine	2.8	1.4	14	19	12	73	18	No survivors							9
2-Chloroethyl morpholine	150	.93	21	14	38	39	34	10		78		6			17

* Values between brackets not quantitatively reliable because lesions were not uniform throughout testes (see section: Pathological Changes Following Nitrogen Mustards).

many types of toxic testicular damage,[12] but in the case of these three nitrogen mustards, at least, it is considered that the early stages of the lesion showed a progression from fusing spermatocytes to these multinucleate giant cells, and fused spermatids were not recognized.

Marked acellularity, with only a few spermatogonia situated peripherally between the Sertoli cells, occurred in a small number of tubules during these early stages, apparently again the result of the failure of new spermatogenic cells to develop as loosened cells passed down the tubules to the epididymis. The more marked occurrence of this hypocellularity late after large doses of 2-chloroethyl morpholine or repeated doses of methyl-bis (2-chloroethyl) amine is discussed later.

Although a complete sequence of cell changes from apparently normal secondary spermatocytes to large syncytial giant cells, and then through all stages of cytoplasmic degeneration and nuclear pyknosis to large hyaline masses with chromatin remnants, could be seen in many testes, especially on the third and fifth days, giant spermatocytes were also formed at the same times and slightly later as a result of the growth of cells without cell division. As early as twenty-four hours after exposure, many of the spermatogonia and spermatocytes still in situ were clearly larger than normal; this change may represent the effect of these drugs on a relatively specific stage of differentiation or division, because these cells tended to disappear and then to reappear during the wave of reparative cell division, which usually started on the third day. At this time, numbers of abnormally large cells of all types appeared, with secondary spermatocytes most numerous, and the majority of the many spermatogonial prophases seen showed clumping and swelling of the chromatin strands.

Twenty-five cells of each of the following types were measured with an ocular micrometer in a section taken seventy-two hours after 150 mg. per Kg. of 2-chloroethyl morpholine, and in a control section. The results are expressed in microns as average cell diameters, plus or minus two standard deviations.

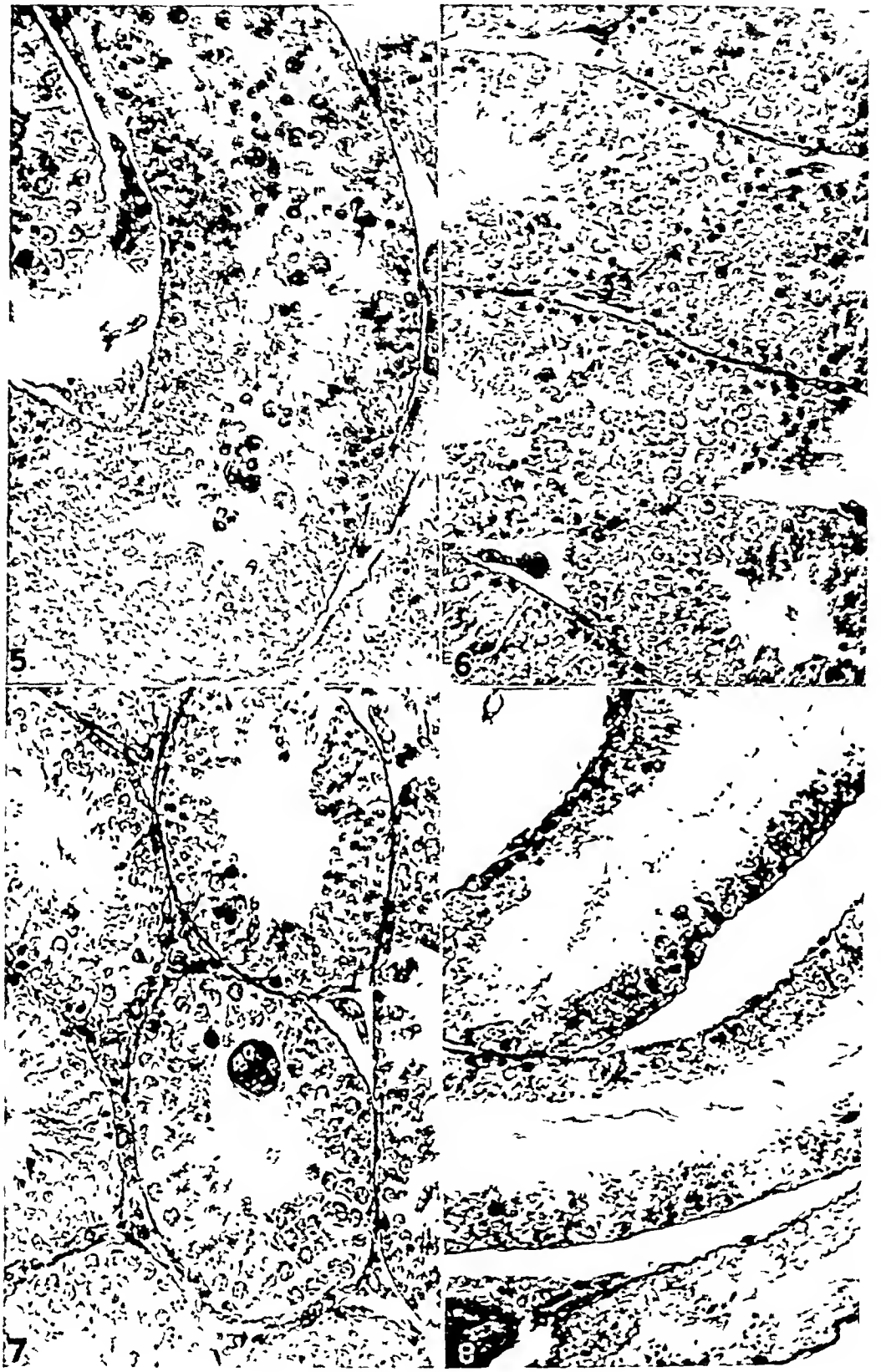
TABLE 3

CELL DIAMETERS 72 HOURS AFTER 150 MG./KG. 2-CHLOROETHYL MORPHOLINE

	Spermatogonia	*Spermatocytes*	
		Primary	*Secondary*
Control	23.4 ± 0.6	29.7 ± 0.8	23.1 ± 0.4
2-Chloroethyl morpholine	27.5 ± 1.0	37.8 ± 0.8	26.4 ± 0.7
p	0.0001	0.0001	0.00015

As can be seen, this increase in size is significant for all three cell types, and the primary spermatocytes, the stage of spermatogenesis during which the most rapid increase in cell volume occurs,[1] were more markedly affected than were the spermatogonia or secondary spermatocytes. Spermatids were not measured because of the small number present at this point in the damage process, and because of their tendency to an asymmetric shape. This cell enlargement, although possibly related in some way to the mechanism(s) known to produce abnormally large cells in amphibian embryos and yeasts exposed to mustards,[3, 8] again cannot be regarded as a specific mustard effect on the testis, having also been observed in conditions of metabolite deficiency.[10] During the early stages of the repeated injection of methyl-bis (2-chloroethyl) amine, small numbers of Sertoli cells were noted to be unusually large and globular, but this process did not continue.

Rather rarely, and usually after the third day, lobulation and fragmentation of the nuclei of the larger cells were seen; these very large cells could usually be seen in a number of adjacent serial sections, in some of which they appeared multinucleate, the size of the nuclei varying, and in some of which they had lobulate nuclei. Although, as stated above, the primary spermatocytes appeared to have the greatest tendency to become abnormally large, and the nuclei of the majority of these later giant cells resembled those of resting primary spermatocytes, the nuclei of some showed the central nucleoli, without surrounding vacuoles, of secondary spermatocytes. In a few of these cells, nuclei or lobes



(*For captions see opposite page*)

of nuclei of both types could be seen. It is significant that much smaller numbers of similar cells with lobulate nuclei, as well as small numbers of abnormally large secondary spermatocytes resembling those seen during the early regenerative period, were seen in fasted control animals, but not in normal controls.

The still later changes produced by 2-chloroethyl morpholine and by repeated small doses of methyl-bis (2-chloroethyl) amine leading to extreme hypocellularity of the spermatogenic tissue, with the tubules lined largely by Sertoli cells (Fig. 5), may be summarized as continuations of the various processes already described—mitotic arrest followed by pyknosis and degeneration, direct cell lysis, abnormal cell growth followed by lysis, giant-cell formation with eventual degeneration, cell fusion followed by degeneration, and disorganization and fragmentation of spermatogenic tissue with loss of sloughed cells via the epididymis.

After the period of rapid degeneration just described, the recovery process in all cases was characterized by a gradual loss of abnormal cells, and a gradual increase in the number of normal ones (Figs. 6, 7). Functional recovery with formation of mature sperm, seen by the end of the period of study (two to three weeks after injection) for all doses of all three compounds that allowed survival of this duration, occurred before the number of spermatogenic cells in the tubules had returned to normal. Whether all such sperm were normal cannot be said, but fresh preparations showed them to be apparently normally motile, and a small number of mating trials following exposure of both members of the pair to comparable doses of 2-chloroethyl morpholine have been successful.

The observation that during the recovery phase, the hypocellularity following repeated small doses of methyl-bis (2-chloroethyl) amine persisted longest in the peripheral portions of the tubules has been mentioned already; no adequate explanation for this observation presents itself.

Discussion

The significances of the various cellular changes observed have been discussed in the section on pathological observations. These changes are by no means specific for the nitrogen mustards so far as can be told from this study: essentially similar changes are known to follow many other "toxic" processes, for example, roentgen-ray radiation,[6, 16] vitamin deficiency and malnutrition,[7, 10, 12] estrogen overdosage,[2] cryptorchidism,[13] certain doses of androgen,[4, 17] colchicine,[5] administration of pitressin,[15] and exposure to a large number of poisonous chemicals. The processes of testicular degeneration described after these and other damaging factors differ essentially only in rate and sequence, many degenerative stages in the more rapid processes being obscured by overlapping cell changes or by massive epithelial sloughing, but all the stages of degeneration seen in the testes examined in this study have been described following one or more of these other agents. That similar changes have been reported to occur in malnutrition and specific metabolite deficiencies may be an indication that metabolite deficiency plays a role in the production of these lesions, particularly in view of the known powerful enzyme-inhibiting action of the mustards.

Repeated small doses of methyl-bis (2-

FIG. 5. *Seventy-two hours after injection of 4.0 mg./Kg. of methyl-bis (2-chloroethyl) amine. Note sloughed spermatocytes in the lumen of section of a tubule showing relatively little damage.*

FIG. 6. *Twenty days after injection of 4.0 mg./Kg. of methyl-bis (2-chloroethyl) amine. Note very active mitosis in spermatogonial layers, large numbers of secondary spermatocytes, and small number of spermatozoa.*

FIG. 7. *The same as Fig. 6. Note persistence of damaged cells in small numbers in some tubules.*

FIG. 8. *Twenty days after injection of 150 mg./Kg. of 2-chloroethyl morpholine. Note marked hypocellularity of tubules, with rare spermatogenic cells along the basement membrane.*

chloroethyl) amine produced more severe late testicular damage than a single injection of the same total amount of drug, but evidences of recovery were still noted within two weeks after the end of the series of injections, and it is not known whether a dose schedule capable of producing enough testicular damage completely to prevent testicular regeneration can be devised. No evidence that this is possible, short of relatively high lethal doses, was obtained from this study, which further does not indicate that the testis is relatively more susceptible to the toxic effects of nitrogen mustards given in this way than are other tissues affected by these compounds (lymphoid tissue, bone marrow, intestinal mucosa, kidney). From the clinical point of view, at least, sufficient recovery of spermatogenic function to give some formation of mature and motile sperm was observed by the end of a four-week period after injection of all three compounds for all nonfatal single, or repeated, dose levels used.

SUMMARY

Testicular lesions were observed in mice following intraperitoneal injection of nine nitrogen mustards, and testes of young adult mice were studied in detail at various times after injection of three of these. Acute and chronic degenerative changes essentially similar to those known to follow metabolite deficiency, roentgen-ray radiation, and exposure to many other chemicals, were observed. Following all nonfatal single or repeated doses studied, for all three compounds, recovery of spermatogenic function to the point of mature sperm formation occurred by four weeks after exposure.

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NITROGEN MUSTARDS

Statistical Analysis of Effects on Sarcoma 180 and Viscera of Normal Mice in Relation to Toxicity and Structure

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THE following study was conducted in order to assess the significance, and interchangeability, of results obtained by various methods of screening compounds for chemotherapeutic activity against tumors, and to compare the degree of activity of a series of related nitrogen mustards against a solid tumor and against the various susceptible normal tissues. It was further desired to analyze both these factors in terms of the toxicity and structure of the various compounds studied. To accomplish this, the data in a previous paper[1] on the results of studying a series of thirty-six nitrogen mustards by five different methods of estimating effect on mouse sarcoma 180, data on the effects of these compounds on the viscera of normal mice prepared by Landing et al.[3] and the data of Goldin et al.[2] on their toxicity in mice were subjected to analysis.

The various compounds studied by each of the five methods of estimating effects on sarcoma 180 were categorized in three groups on the basis of production of positive, doubtful or intermediate, or negative effects, and the results by each method were compared to those by each other method. The effects on tumors by the five methods listed were compared to the effects on the weight and viscera (lymphoid tissues, bone marrow, testis, gastrointestinal mucosa, white blood-cell count) of normal mice; to the toxicities of the agents used (median lethal dose (LD_{50}) in micromoles per Kg.; to the maximum tolerated cumulative dose in micromoles per Kg.; to the maximum tolerated cumulative dose as a fraction of the median lethal dose); and to the chemical structure. The variables studied, and the categories used, are included in Table 1. The effects of the individual compounds on tumors by the various methods of study, and toxicity data, are given in the paper of Shapiro et al.; additional toxicity data and data on the effects of these compounds on the organs of normal animals are given in the references already mentioned.

A summary statement of the statistical treatment of the data is as follows: All of the compounds were assigned to their proper classes in Table 1 for each of the various methods studied. For a group of compounds studied by any two of these fifteen methods, tabulations of the above kind became the border totals of a 3×3 table. The rest of such a 3×3 table was completed by filling out the nine cells in accordance with each compound's dual classification for the variables studied. Then the degree of correlation between the two variables was determined by deriving the Pearson coefficient of correlation. In so doing, it was assumed that the three classifications for any variable were numerically one unit apart on a continuous axis of effect† and that the correlation coefficient derived could be interpreted in the light of the sampling distribution of a correlation of zero for small samples.

The results of this analysis are given in Fig. 1. Table 2 lists the variables studied in order of the number of significant correlations with other variables.

The tables are subject to the following

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† The effect of the arbitrary scaling has been tested by determining the correlation coefficient under the assumption of a normal distribution. The correlation coefficients obtained under this new scale (that is, the probit scale) were essentially the same as those obtained above. Therefore any correlation called significantly different from zero would not be influenced by the scale chosen.

TABLE 1

CLASSIFICATION OF NITROGEN MUSTARDS FOR STATISTICAL ANALYSIS OF TOXICITY, STRUCTURE, VISCERAL EFFECTS, AND EFFECTS ON SARCOMA 180

Properties of compounds studied	*Classes*		
	1	*2*	*3*
*Positive Effects on Tumors**			
Repeated small doses, H. & E. sections	−	±	+
Repeated small doses, orcein smears	−	±	+
Single large doses, H. & E. sections	−	±	+
Single large doses, orcein smears	−	±	+
Decreased tumor weight (significance as compared to control series)	$P>.05$	$.01<P<.05$	$P<.01$
Positive Effects on Mice†			
Weight loss*	0% or gain	0-10%	10%+
Lymphoid-tissue damage	− ±	+	++ etc.
Bone-marrow damage	−	±	+ etc.
Gastrointestinal epithelial damage	−	±	+ etc.
Testis damage	− ±	+	++ etc.
Significance of white-count depression	$P>0.046$	$0.046>P>0.0027$	$P<0.0027$
Toxicity‡			
LD_{50}-median lethal dose (micromoles/kilo)	300+	300 to 25	25 or less
Maximum tolerated cumulative dose (micromoles/kilo)	10+	10 to 3	0 to 3
Fractional maximum tolerated cumulative dose (fraction of LD_{50})	50%+	49% to 15	15% or less
Chemical structure (2-chloroethyl)	mono-	bis- and tris-	tetra- or more

* See Shapiro et al. for techniques, method of estimating effects on tumors, and cumulative toxicity values, and for nitrogen mustards administered and studied in this manner.

† See Landing et al. for techniques, method of estimating effects, and tables of effects on viscera produced by the various agents studied.

‡ See Goldin et al. for techniques and toxicity determinations, and median-lethal-dose values for the compounds used.

interpretations, assuming the validity of the input data, that the classifications used in the analysis are significant, and that the compounds compared for each variable are sufficiently representative of the total population of mustards.

The various visceral effects correlate well with each other, indicating that there is probably no significant tendency for the various nitrogen mustards to damage some of the susceptible organs and not others. The bone marrow, gastrointestinal epithelium, and circulating white blood cells, furnish the most reliable indexes of visceral nitrogen-mustard damage, possibly because of the hypersensitivity and tendency to nonspecific response of the lymphoid system and testis. The various visceral effects correlate less well with the toxicity factors than with each other; the general indication, however, is that the more toxic mustards produce more damage to these particular viscera than nontoxic ones, when both are given in doses equivalent in terms of lethality. The various visceral effects also correlate to some extent with the results of the five methods of studying tumors, indicating that, for this tumor and these mustards at least, greater tumor damage is obtained with the compounds producing more visceral damage, and hence with the more toxic compounds. Conversely, as far as this study goes, the ability to cause visceral damage (in particular bone marrow, gastrointestinal epithelium, and peripheral-blood white-cell damage) is the best index of the ability of a nitrogen mustard to damage sarcoma 180 when given in the same dose, so that for this tumor in mice, the nitrogen mustards have no significant therapeutic index.

Similarly, the various toxicity factors correlate well with each other. Hence, the more toxic mustards (i.e., those with a lower median lethal dose) have a lower maximum tolerated cumulative dose, and also a lower fractional maximum tolerated cumulative

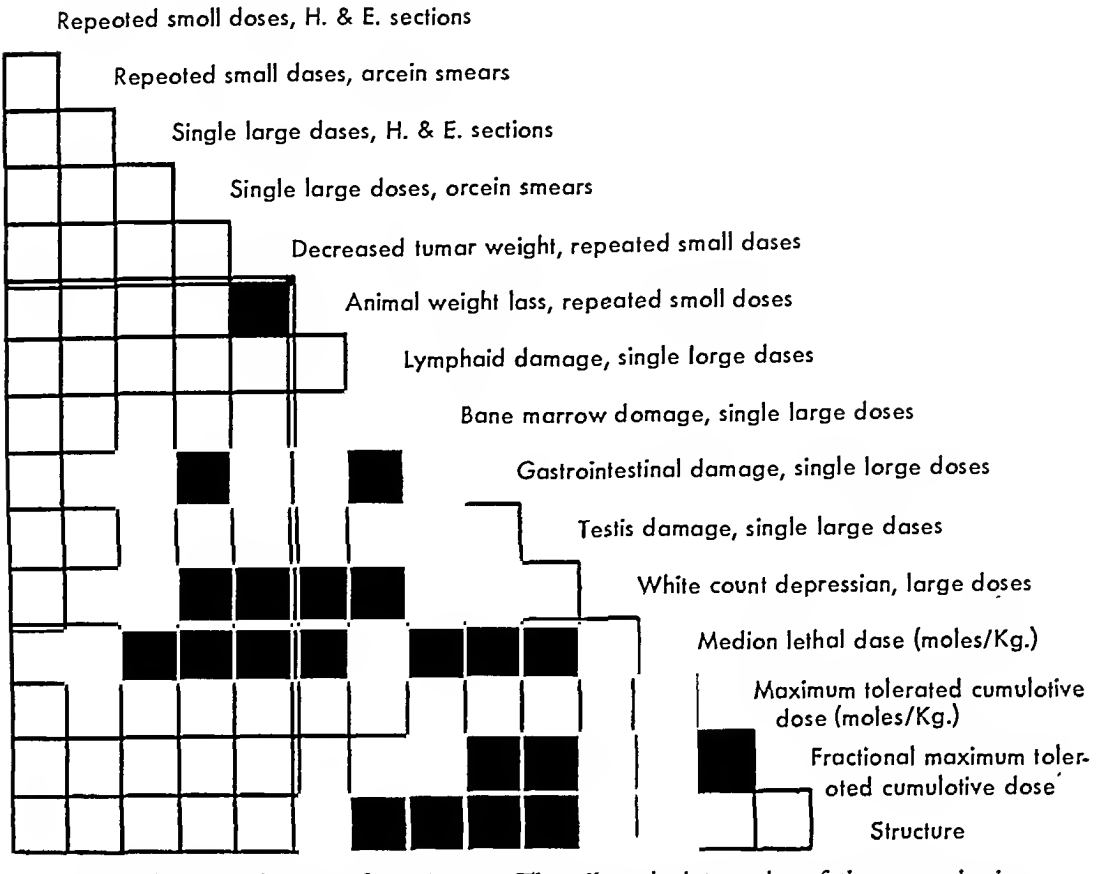

FIG. 1. *Summary diagram of correlations. The cell at the intersection of the row and column opposite any two variables selected indicates the correlation of the variables. Solid square = Correlation significantly different from zero—at the 5 per cent level of significance. White square = No significant correlation demonstrated.*

dose; the more toxic mustards can thus be tolerated in repeated small doses only at smaller fractional doses of the LD_{50} than can nontoxic ones, indicating that the cumulative action of the more toxic mustards is more effective. Further, since the more toxic mustards have greater numbers of 2-chloroethyl side chains, such compounds are more effective in producing visceral and tumor damage than are mustards with fewer 2-chloroethyl side chains. This is in essential agreement with the findings of Burchenal on rat leukemia.

On the other hand, the five methods of studying tumors show no significant relation to each other. These various tumor methods are thus not interchangeable as methods of screening compounds for effect on this tumor; this finding is analyzed in greater detail in the paper of Shapiro et al. Since methods that seem to give results most nearly related to other properties of the mustards correlate predominantly with visceral effects, the results of this analysis indicate that the more toxic compounds, i.e., those with more 2-chloroethyl side chains, are most effective in producing tumor damage. By this method, the tumor behaves essentially like a normal susceptible tissue. Since, further, no evidence was found that this tumor is more sensitive to the action of any of the mustards than are the normal susceptible tissues, the indications are that the cytotoxic action of the mustards on neoplastic tissue, assuming sarcoma 180 to be a representative neoplasm, may in general be exerted by the same mechanisms as is that on normal susceptible tissues.

Since the repeated small-dose hematoxylin-

TABLE 2

VARIABLES STUDIED, IN ORDER OF NUMBER OR SIGNIFICANT CORRELATIONS WITH OTHER VARIABLES

(Maximum total = 14)

Variable	*Significant correlations*
Median lethal dose	6
Significance of white-count depression	6
Bone-marrow damage	5
Gastrointestinal epithelial damage	5
Fractional maximum tolerated cumulative dose	4
Chemical structure	3
Animal weight loss	3
Effect on tumors, single doses, H. & E.	2
Lymphoid damage	2
Maximum tolerated cumulative dose	2
Tumor weight loss	2
Testis damage	1
Effect on tumors, repeated doses, orcein smears	1
Effect on tumors, repeated doses, H. & E.	0
Effect on tumors, single doses, orcein smears	0

cosin–section and aceto-orcein–smear methods, and the single large-dose aceto-orcein–smear method, of studying tumors showed poor correlation with the other effects of these mustards, the significance of their end points, and thus of results obtained using them, must be questioned. However, no data are available that allow an evaluation as to which if any of the five methods used in this study gives results translatable to human tumors. As far as can be told from this study, the statement that a particular screening program finds a certain compound to be active against the test tumor cannot be extended to other programs in the absence of additional knowledge as to the correlation between results by the two methods.

SUMMARY

1. Statistical analysis of data on the toxicity, structure, tissue effects, and effects on mouse sarcoma 180, of a series of nitrogen mustards, indicates that compounds with a greater number of 2-chloroethyl side chains (total range of 1 to 4) are in general more toxic than those with fewer 2-chlorocthyl side chains. More toxic nitrogen mustards are in general more effective in damaging both sarcoma 180 and the normal susceptible tissues (lymphoid tissue, bone marrow, gastrointestinal epithelium, circulating white cells, testis) than are less toxic compounds given at the same fraction of the lethal dose. The effects on the tumor correlate fairly well with the effects on normal animals, so that these latter furnish fairly reliable indexes of potential antitumor action. No evidences of a therapeutic ratio—namely, that this tumor is more susceptible to the cytotoxic action of these mustards than the normal susceptible tissues—were found.

2. Visceral effects correlate fairly well with each other, as also do the toxicity factors. However, the results of the five methods of studying tumor effect show insignificant correlation with each other. These methods thus seem to be independent, and results obtained by one type of screening technique cannot be compared to those obtained by another, without prior knowledge of the degree of correlation of the results of the two techniques.

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PRELIMINARY STUDIES ON THE CLINICAL TOXICITY OF 5-AMINO-7-HYDROXY-1-*v*-TRIAZOLO[*d*]-PYRIMIDINE (GUANAZOLO)

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Clinical interest in 5-amino-7-hydroxy-1-*v*-triazolo[*d*]pyrimidine[4] was aroused by the report of Kidder, Dewey, Parks, and Woodside,[2] that this compound caused definite inhibition of growth in mice of a transplantable mammary adenocarcinoma, Eo771. A prior article by Kidder and Dewey[1] had shown that this substance was a potent antagonist of guanine in the metabolism of the ciliate, *Tetrahymena geleii*. Because of the possible value of the drug in the therapy of human tumors, preliminary toxicity studies were done on rats and dogs in the Department of Pharmacology,[3] and the compound was then administered in eight cases of radiation-resistant cancer. The purpose of this preliminary note is to describe certain toxic reactions resulting from the use of the drug.

Since little is known of the absorption of the compound when given by mouth, and because toxicity studies had all been based on parenteral dosage, it was decided that the drug should be given intravenously. In order to produce a solution that could be administered in such fashion, an equimolar quantity of sodium hydroxide was added to 5-amino-7-hydroxy-1-*v*-triazolo[*d*]pyrimidine† and the latter made up in concentration of 5 mg. per cc. in physiological saline solution. It was usually injected in daily doses of 200 mg. each. The drug was also available in capsules for oral use.

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†We are indebted to the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, New York, for supplying the drug for clinical use.

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All seven cases receiving the drug parenterally developed a toxic dermatitis after total doses varying from 400 to 1950 mg. had been given (Table 1). The rashes differed one from another only in severity, not in general appearance. A crop of bright red macules formed over the cheeks, shoulders, arms, forearms, chest, back, abdomen, and legs (Fig. 1). The dorsa of the hands and feet were frequently involved, leaving the palms and soles free. The rash speedily became maculopapular and confluent and, in the more severe cases, developed vesicles and small bullae, chiefly over the buttocks. Such cases progressed in about a week to marked desquamation, which, however, was completely lacking in the mild cases. A moderate to severe burning sensation was present whenever the rash was florid. Itching was present to slight degree in only one case. During the second week, the color became brown, and then gradually faded over a period of at least four weeks. A single patient who received the drug by the oral route only failed to develop a rash. Those who were given the compound orally following the onset of the rash from intravenous dosage did not have exacerbations of their lesions despite the fact that the daily dosage administered by the oral route was many times as great as that given parenterally.

Gastrointestinal symptoms were frequent following either oral or parenteral administration. Nausea and vomiting were common, and in two cases diarrhea was severe enough to cause discontinuance of medication, following which the symptoms promptly disappeared. Neither intravenous nor intramuscular injections caused local pain or other reaction.

Complete blood studies, including platelet

TABLE 1

TOXIC MANIFESTATIONS OCCURRING IN PATIENTS TREATED WITH GUANAZOLO

Patient Age Diagnosis	Azoguanine		Dermatitis						Gastrointest. symptoms		
	Dose by course (mg.)	Route	Onset	Macules	Bullae	Desquamation	Burn. sensat.	Durat. days	Nausea	Vomit.	Diarrhea
B.S. 31 Osteogen. sarcoma	1—1950 2—1000	i.v. i.v.	1950 mg. in 6 doses	++ ++++	0 ++	++ +++	0 +++	18+	++ +++	++ +++	0 0
J.F. 39 Ca., breast	1—1000 2—600 3—9000	i.v. i.v. oral	400 mg. in 2 doses	++ +++	0 0	+ +	+ ++	25+	++ +++ +++	++ +++ +++	0 0 ++
N.W. 58 Ca., tongue	1—1000 (1 dose) 2—1000 (1 dose)	i.v. i.v.	1000 mg. in 1 dose	++ +++	0 0	0 0	? ?	4+	0 0	0 0	0 0
D.G. 41 Embryo. ca., testis	1—1400 2—400 3—3000	i.v. i.v. oral	1400 mg. in 6 doses	++ +++	0 0	0 0	+ ++	9+	++ +++ +	+ + 0	++ +++ +++
P.M. 16 Embryo. ca., unk'n orig.	1—2200 2—7500	i.v. oral	1000 mg. in 5 doses	++	0	0	0	24+	++ ++	++ ++	0 0
A.P. 57 Ca., breast	1—1000 2—47,000	i.v. oral	1000 mg. in 5 doses	++	++	++	0	17+	++ 0	++ 0	0 0
R.F. 55 Ca., lung	1—17,050	ora	0	0	0	0	0	0	0	0	0
K.B. 53 Ca., breast	1—650	i.m.	650 mg. in 4 doses	+	0	0	0	1+	0	0	0

counts, were made at frequent intervals, but no consistent change occurred. Bone-marrow aspirations done in five cases before and after treatment showed no change. Serum alkaline phosphatase, likewise determined before and after therapy, showed no definite trend.

No subjective or objective improvement has been seen in any of these patients up to the present time, but sufficient time has not as yet elapsed since the institution of therapy to allow accurate evaluation. A report covering therapeutic considerations will be published at a later date.

SUMMARY

A maculopapular rash developed in all patients given 5-amino-7-hydroxy-1-*v*-triazolo[*d*]pyrimidine parenterally. In some cases the rash progressed to the vesicular stage and was followed by desquamation. Oral dosage with the drug caused no rash and failed to produce exacerbation of existing dermatitis. Nausea, vomiting, and diarrhea, were common with either oral or parenteral administration. The bone marrow and peripheral blood were not affected by the drug in the doses given.

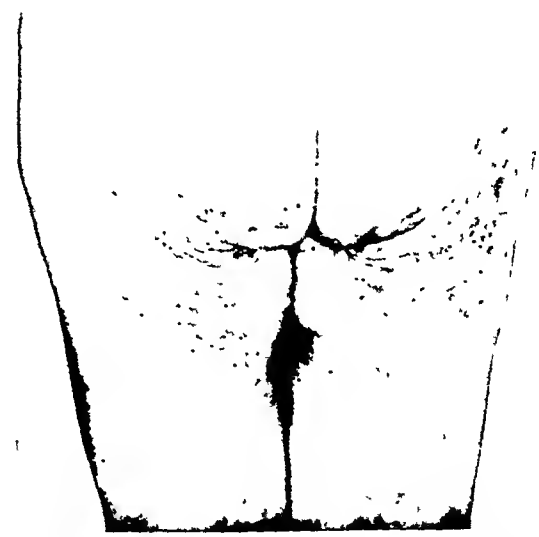

FIG. 1. *Typical rash six days after onset. Vesiculation preceded the desquamation shown here.*

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LABELED INORGANIC SULFATE IN THE DIAGNOSIS OF CARTILAGINOUS TUMORS AND THEIR METASTASES

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WITH THE TECHNICAL ASSISTANCE OF
DORIS R. FRANKEL, B.SC.

IT has been shown by Singher and Marinelli and confirmed by Dziewiatkowski that sulfate administered to the rat is retained mainly by the bone marrow, bone, and cartilage. Since Greene had described a case of chondrosarcoma that had been improperly diagnosed by the classical methods but that appeared to be cartilaginous when grown in the anterior chamber of a guinea-pig eye and was shown at autopsy to be chondrosarcoma, it was thought that a determination of the differential fixation of labeled sulfate might be a valuable, rapid, confirmatory test in the diagnosis of cartilaginous tumors and their metastases.

Since the long-term physiological effects of radioactive sulfur are unknown, and since very high specific activities would be necessary if the tumors were to be studied in vivo, it was decided that the method of in vitro tissue culture should be investigated. Previous work by the author had shown that embryonic chick cartilage when cultured in a nutrient medium containing labeled sulfate would concentrate the sulfate and retain it in a form insoluble in warm isotonic salt solution, hence there was reason to believe that the rapidly growing cartilage tumor tissue might behave similarly.

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This investigation was made possible by a grant from The Nutrition Foundation, Inc., for the study of the in vitro nutrition of normal and abnormal tissues.

The investigation was aided in part by a grant to the Department of Preventive Medicine. The Johns Hopkins Medical School, by the American Cancer Society upon recommendation of the Committee on Growth of The National Research Council.

The radioactive sulfur used in this investigation was obtained from the Oak Ridge Laboratory, Carbide and Carbon Chemicals Corporation, on allocation by by the United States Atomic Energy Commission.

The human normal and tumor tissues used in this investigation were provided through the co-operation of D. O. Chrisman, M. D. Resident in Orthopedics, The Johns Hopkins Hospital. The diagnoses were transmitted to us by the Department of Surgical Pathology, The Johns Hopkins Hospital.

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METHOD

Biopsy samples of tissue were taken from the center of the tumors, the periphery, the neighboring normal tissue, and occasionally from the neighboring muscle; the fresh materials were placed in labeled test tubes containing sterile Tyrode's solution, and then taken to the tissue-culture laboratory for preparation. Each sample of tissue was divided into smaller samples weighing approximately 10 mg. for the most consistent results, and weighed to the nearest 0.2 mg. on a sterile platinum wire on the Roller-Smith Precision Balance. Each tissue fragment was dropped into a numbered test tube containing 2 ml. of either bovine serum ultrafiltrate or Tyrode's solution to which had been added sodium sulfate labeled with radioactive sulfur, S^{35}. The tubes were stoppered with rubber stoppers and incubated in stationary racks at 38° C. Samples were run occasionally at 2° C. After thirty-six hours, the tubes were removed from the incubator, examined for bacterial contamination, and then washed with a total of 50 ml. of isotonic sodium sulfate solution, each 10-ml. portion of the washing solution being permitted to drain through the filter before the next portion was added.

The tissue from each tube was then covered with 250 mg. of anhydrous sodium carbonate in a platinum crucible and heated at the fusion temperature of sodium carbonate for ten minutes. The crucible was allowed to

cool, and the fused mass dissolved in 20 ml. of dilute hydrochloric acid. The *p*H was adjusted to 5 with NaOH, and the resulting solution then made up to approximately 30 ml. in volume; 5 ml. of 0.05 normal unlabeled sodium sulfate was added and the solution heated to the boiling point. The sulfate was precipitated by the addition of 3 ml. of half molar $BaCl_2$ solution, the beakers covered with watch glasses, and the precipitates permitted to sit at 60° to 70° C. for two hours for crystal growth. After digestion, the precipitates and supernatant solution were transferred to 40-ml. centrifuge tubes with conical bottoms, and centrifuged. The precipitates were washed twice with 30 ml. portions of slightly acidified distilled water and finally with 20 ml. of 70 per cent alcohol. The washed precipitates were then transferred quantitatively to weighed counting pans* by washing the centrifuge tube with small portions totaling 5 ml. of 80 per cent alcohol solution. The pans were placed on an electric hot plate at approximately 65° C. and permitted to evaporate to dryness. They were then dried in an electric oven at 110° C. for twenty minutes, cooled in a desiccator, and weighed. The weight of $BaSO_4$, determined by difference, was later used to correct the counting data for self-absorption or mechanical loss of the precipitate.

All of the counting data were obtained by the use of a Geiger-Müller tube with a thin mica end window. The counting data were corrected for background count and self-absorption to 30 mg. $BaSO_4$, and were obtained with a precision of ±5 per cent. Data are given in the tables as counts per 100 mg. of wet tissue. These values were obtained by dividing the corrected average count for each sample by the wet weight of the sample and multiplying by 100. The figures in the tables are average values for several individual cultures of each of the original tissue samples.

In using the tables of data, the reader must keep in mind the fact that the data for the different patients were obtained by culturing the tissues on media containing sulfate of different specific activities, and hence the differential absorption of sulfate applies only to the other tissues of the same patient.

Case Reports

Case 1. Patient E.L., a colored woman, aged 45 years. Biopsied March 17, 1949.

The preliminary surgical diagnosis was chondrosarcoma of spine.

Weighed tissue fragments were cultured in plasma clot covered with 2 ml. of Tyrode's solution containing 10 micrograms per ml. of sulfate with a specific activity of 500 counts per microgram referred to 30 mg. of $BaSO_4$ carrier. (Table 1.)

The preliminary diagnosis was not confirmed, but the tumor could not be typed by the pathologists.*

Table 1

Origin, tissue sample	*Appearance*	*Averaged values for insol. fixed sulfate counts/min./ 100 mg. wet tissue*	*Biochemical indications (differential absorption of sulfate)*
Normal cartilage		209	
Normal bone		441	
Abnormal tissue surrounding tumor	Mixed tissue	136	
Periphery of tumor	Pasty white	74	Noncartilaginous
Center of tumor	White soft tissue	37	Noncartilaginous

Case 2. Patient M.C., a white woman, aged 47 years. Biopsied March 18, 1949.

The preliminary surgical diagnosis was chondrosarcoma of vertebra.

Weighed tissue fragments from various surgical samples were cultured in bovine serum ultrafiltrate labeled with 20,000 counts per ml. of carrier-free radioactive sulfate as received from the Oak Ridge Laboratory of the Atomic Energy Commission. (Table 2.)

Table 2

Origin, tissue sample	*Appearance*	*Averaged values for insol. fixed sulfate counts/min / 100 mg. wet tissue*	*Biochemical indications (differential absorption of sulfate)*
Periphery of tumor (fascia)		338	
Center of tumor	Bone; tissue was calcified	902	Bone
Center of tumor	Cartilaginous	3,060	Cartilage
Center of tumor	White pasty	68	Noncartilaginous
Center of tumor	Mixed tissue	239	Noncartilaginous
Normal muscle		413	

*Seamless tin boxes of one-fourth–ounce capacity with paper labeled lids obtained from The Buckeye Stamping Co., Columbus, Ohio.

*The pathologists had no knowledge of our investigation, and hence the chemical data were not considered in the diagnoses.

The final diagnosis (tentative) was neurosarcoma.

The gross appearance indicated the tumor to be ossifying cartilaginous tissue. The biochemical findings would indicate a tumor containing osseous, cartilaginous, and noncartilaginous tissue. The noncartilaginous tissue had a relative sulfatc absorption similar to the nervous tissue of the chick, but the chemical findings did not fully support the pathologist's opinion.

Case 3. Patient J.D., a white man, aged 60 years. Biopsied March 28, 1949.

The preliminary surgical diagnosis was ossifying chondrosarcoma of the right ischium.

Weighed portions of the surgical matcrial were cultured in bovine serum ultrafiltrate labeled with 140,000 counts per ml. of carrier-frec sulfate, rcferred to 30 mg. of $BaSO_4$ precipitate. (Table 3.)

The final diagnosis was osteogenic adcnocarcinoma.

TABLE 3

Origin, tissue sample	*Appearance*	*Averaged values for insol fixed sulfate counts/min / 100 mg. wet tissue*	*Biochemical indications (differential absorption of sulfate)*
Musele of right ischium		215	
Center of tumor	Cartılaginous tissue	1,561	Cartılaginous
Periphery of tumor	*Spongy red bone*	*1,160*	*Bone*

Case 4. Patient P.M., a white boy, aged 14 years. Biopsied March 31, 1949.

The preliminary surgical diagnosis was osteochondroma of the proximal right tibia.

Weighed portions of the surgical material were cultured in a medium of bovine serum ultrafiltrate having the same activity as for case 3. (Table 4.)

The final diagnosis was osteochondroma.

TABLE 4

Origin, tissue sample	*Appearance*	*Averaged values for insol fixed sulfate counts/min / 100 mg wet tissue*	*Biochemical indications (differential absorption of sulfate)*
Periphery of tumor		5 300	Cartılagmous
Periphery of tumor (possibly normal bone)	Bony	854	Bone
Center of tumor	Spongy bone	1,517	Spongy bone
Periphery of tumor	Cartılaginous	12,000	Cartılage
Soft tissue, normal fascia		2,562	
Periphery of tumor (kept at 2° C. as control)	Cartılaginous	110	
Normal bone of knee		983	
Normal cartılage of knee		4,275	

Case 5. Patient B.A., a white man, aged 67 years. Biopsied April 28, 1949.

The preliminary surgical diagnosis was osteosarcoma of right clavicle.

The samples of tissue obtained from surgery were divided into smaller portions which were weighed and cultured in 2 ml. of Tyrode's solution containing 36,000 counts per ml. of carrier-free sulfate as obtained from Oak Ridge. (Table 5.)

The final diagnosis was plasma-cell myeloma with ossification at the margins of the tumor.

TABLE 5

Origin, tissue sample	*Appearance*	*Averaged values for insol. fixed sulfate counts/min./ 100 mg. wet tissue*	*Biochemical indications (differential absorption of sulfate)*
Center of tumor	Mixture of soft tissue	844	Not bone or cartılage
Center of tumor (kept at 0° C. as control)	Soft tissue	299	
Periohery of tumor	Hard bone	69,000	Bone
Periphery of tumor (kept at 0° C. for control)	Hard bone	85	
Normal muscle		965	
Normal muscle (kept at 0° C. as control)		61	
Normal muscle fascia	Thick yellow tissue dissected from normal musele sample	2,210	

Case 6. Patient R.R., a white boy aged 14 years. Biopsied May 5, 1949.

The preliminary surgical diagnosis was osteogenic sarcoma.

Small portions of the surgical samples were weighed and cultured in Tyrode's solution containing 36,000 counts per ml. of carricr-free sulfate as obtained from Oak Ridgc. (Table 6.)

The final diagnosis was osteochondrogenic tumor of osteoblasts and giant cells.

TABLE 6

Origin, tissue sample	*Appearance*	*Averaged values for insol. fixed sulfate counts/min./ 100 mg. wet tissue*	*Biochemical indications (differential absorption of sulfate)*
Center of tumor	Cartılaginous and bony	3,668	Cartılaginous
Periphery of tumor	Cartılaginous and bony	3,800	Cartılaginous
Normal bone		9,940	
Normal muscle		316	

RESULTS AND DISCUSSION

The results of the six preliminary experiments in which adult human tissues were maintained in tissue culture in the presence

of inorganic sulfate labeled with radioactive sulfur show that human normal and tumor tissues exhibit characteristic differential affinities for sulfate similar to the normal tissues of the intact rat[1, 4] and very similar to the tissues of the embryonic chick when cultured in vitro.[3]

In the first case, patient E.L., the preliminary diagnosis was not borne out by the differential sulfate fixation, which indicated that the tumor was not cartilaginous in its sulfate metabolism. In this case, the pathologists were unable to determine the type of tumor.

In the second case, patient M.C., the preliminary diagnosis was only partly supported by the differential sulfate fixation of the patient's tissues, the indications being that the tumor contained tissues of mixed origin, part of the central portions being cartilaginous and bony, other portions being white and pasty and having a very low sulfate affinity, similar to nervous tissue of the chick. The tentative final diagnosis was that the tumor appeared to be neurosarcoma. The cartilage and bone may have been normal tissue projecting into the tumor mass; apparently they were not considered in the pathologist's report.

In the third case, patient J.D., the preliminary diagnosis was supported by the differential sulfate fixation, the central portions of the tumor being cartilaginous in appearance and sulfate metabolism, the periphery showing ossification. The final diagnosis was partly supported, but the cartilaginous nature of the tumor was not included in the final diagnosis.

In the remaining three cases the differential sulfate fixation of the tissues supports both the preliminary and the final diagnosis of the tumor type. In none of the diagnoses were the pathologists informed of our investigation or the chemical findings.

Upon examination of the data for the various tissues on the different culture media, it was seen that the most significant differences in the sulfate fixation of the tissues were to be found when the culture medium was Tyrode's solution to which had been added the carrier-free sulfate as obtained from the Atomic Energy Commission Laboratory at Oak Ridge, Tennessee. For those wishing to use the method, it is suggested that the labeled sulfate of maximum specific activity be added to that portion of the Tyrode's solution containing the dextrose, and autoclaved. An adequate final activity for the modified Tyrode's solution is 20,000 counts per ml. referred to 30 mg. of $BaSO_4$ in the counting pan. Refinements in the method were developed in later work with chick tissue and are reported in another paper.[3]

Good results were obtained where no plasma support was provided for the tissue fragments, the fragment being merely covered by the medium in the bottom of an upright stationary test tube. However, somewhat more consistent data were obtained when the tubes were turned slowly in a rotor.

Summary

It has been shown that adult human normal and abnormal tissue maintained in tissue culture for relatively short periods of time in the presence of low concentrations of sodium sulfate labeled with S^{35} in modified Tyrode's solution will exhibit the characteristic differential sulfate fixation or retention originally described by Singher and Marinelli for the tissues of the intact rat.

The determination of the differential sulfate fixation of tumor tissue, normal tissue of the same type, and muscle tissue from the same patient is suggested as a rapid confirmatory test for cartilaginous cancers and their metastases.

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